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IMMUNOLOGIC ASPECTS OF THE SEXUAL CYCLE

I. ANAPHYLACTIC STUDIES WITH MAMMALIAN FOLLICULAR FLUID *

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The interest in the problems of endocrinology and sex physiology during the last decade has resulted in establishing the importance of autacoid substances as body regulators. During this time the analysis of these problems has been almost entirely from a physiologic standpoint, rather than from an immunologic one, owing, no doubt to the fact that the old theory of immunity and species-specificity rather precluded the application of these principles to problems of sex physiology. Gradually, however, new concepts of immunity have been formed which modify somewhat the older theories.

Hektoen,¹ in 1927, brought attention to certain of these newer concepts. He said:

It is of special interest that in connection with fundamental problems of immune specificity and the production of antibodies these nonspecies-specific antigens can evoke the formation of corresponding antibodies in the homologous species, at least under certain conditions. In view of this circumstance may it not be well to subject to renewed scrutiny the old assumption that species-specific antigens are incapable of provoking any antibody response in their own species?

The early work of Wells,² Dale and Hartley³ and Dale and Dakin⁴ distinguishing the various ovoproteins and at the same time, demon-

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1. Hektoen, L.: Observations with the Precipitin Reaction, *J. Immunol.* **14**:1, 1927.

2. Wells, H. G.: Studies on the Chemistry of Anaphylaxis (III), *J. Infect. Dis.* **9**:147, 1911.

3. Dale, H. H., and Hartley, P.: Anaphylaxis to the Separated Proteins of Horse Serum (Note on Anaphylaxis to Pure Egg Albumin), *Biochem. J.* **10**:408, 1916.

4. Dale, H. H., and Dakin, H. D.: Chemical Structure and Antigenic Specificity: A Comparison of the Crystalline Egg Albumin of the Hen and the Duck, *Biochem. J.* **13**:248, 1919.

strating the chemical relationships of the ovoproteins of various species of birds, directed our efforts to what might be considered similar study in the mammal, namely, the immunologic relationship of mammalian follicular fluids.

It is felt that the data here presented lend support to a theory that graafian follicular fluid, the product of granulosa epithelium and probably of the ovum of the guinea-pig, is relatively nonspecies-specific and auto-antigenic, and that the formation of antibodies against it may be responsible for certain cyclic conditions attending that animal in sixteen or seventeen day cycles.

It has been our hope that these conditions in the female guinea-pig may serve in a study of the histologic and physiologic aspects of immunity, a problem suggested to us by Dr. Herbert M. Evans and Dr. Karl F. Meyer.

The first part of the experimental work here reported deals entirely with the immunologic relations of mammalian follicular fluids, and because of the ease in carrying out gross anaphylactic reactions only these reactions were used at this time. We have, however, been interested in studying the sex cycle of the female guinea-pig and in understanding its various stages from an immunologic point of view based on what seems to be an extremely sensitive balance of graafian follicular fluid and antisubstances. Therefore, in the second part of this work, we have continued a study of the gross anaphylactic reactions, representing them graphically by means of the bronchospasm reaction; and have included correlative histologic studies of the ovaries. The Schultz-Dale smooth muscle reaction has lent itself especially well to our purpose, and in the third part, representative charts obtained with this method are reproduced together with the histologic studies. It may be mentioned that this phase of the study is not complete.

GROSS SHOCK AS CRITERION OF HYPERSENSITIVITY

The work reported in this section has to do with the demonstration of (1) the antigenicity of follicular fluid, (2) the antigenic relationship of various follicular fluids and (3) the auto-antigenicity of follicular fluid. Ten healthy guinea-pigs (seven females and three males), weighing from 450 to 500 Gm., were sensitized by the intraperitoneal injection into each of 0.5 cc. of sow's follicular fluid, two or three weeks previous to experimentation. The estrous cycles of the female animals had been observed over a three months' period. The animals were given the critical dose of 0.5 cc. each of sow's follicular fluid intracardially (fourteen days after the last estrus of the females). All the animals went through the classic syndrome of anaphylaxis terminating in death.

Next, five normal male guinea-pigs, weighing 500 Gm. each, were sensitized with 0.5 cc. each of sow's follicular fluid by intraperitoneal

injection. At the end of two weeks, each of these animals received an intracardial injection of 0.5 cc. of cow's follicular fluid. All the animals gave the typical symptoms of anaphylactic shock terminating in death.

To demonstrate the antigenic relationship of mare's follicular fluid to sow's follicular fluid, two normal female guinea-pigs, weighing from 400 to 450 Gm., were sensitized with 0.5 cc. each, of sow's follicular fluid, given intraperitoneally. The critical dose of mare's follicular fluid was given intracardially three weeks after sensitization. Both animals went through severe anaphylactic shock, but eventually recovered. Two normal male guinea-pigs sensitized with 1.5 cc., each, of sow's follicular fluid each received an intracardial injection of 3 cc. of mare's follicular fluid twenty-one days later. Both died with typical anaphylactic symptoms.

To show a similar relationship when the animals were sensitized to one of the other follicular fluids, twelve normal guinea-pigs (each weighing about 500 Gm.) were sensitized with 0.5 cc., each, of cow's follicular fluid, given intraperitoneally. Three weeks later, five of these animals died with typical symptoms of anaphylactic shock following the injection of 0.5 cc., each, of cow's follicular fluid intracardially. Another five died from anaphylactic shock after the intracardial injection of 0.5 cc., each, of sow's follicular fluid. Of the remaining animals, one was given 0.5 cc. of mare's follicular fluid and another 0.5 cc. of sheep's follicular fluid intracardially. The latter died with the classic symptoms of anaphylaxis within five minutes; the first animal, receiving mare's follicular fluid, suffered severe anaphylaxis, but recovered. Five normal male guinea-pigs were then sensitized with 2 cc., each, of cow's follicular fluid, given intraperitoneally. Three weeks later four of these animals suffered severe shock, but recovered after the intracardial injection of 2 cc., each, of mare's follicular fluid; while the remaining one died with typical symptoms following injection of 3 cc. of mare's follicular fluid.

In order to show that the female guinea-pig is auto-immunized to follicular protein and desensitizes itself in cycles, a series of thirty normal adult females was observed over a period of three months with reference to their estrous cycles. These animals were given from 0.5 cc. to 2 cc., each, of sow's follicular fluid, intracardially, on various days of the cycle. No primary shock could be demonstrated in animals from the first to the tenth day of the cycle. Typical anaphylactic shock was demonstrated in animals from the tenth to the last day of the cycle. The anaphylaxis was especially acute, ending in death, in animals that received injections on the last day of the cycle. At autopsy, such animals showed extreme congestion of the uterus, ovaries and mammary glands, as well as the typical emphysematous condition of the lungs.

To further check these results, fifteen female animals, previously sensitized to sow's follicular fluid, were given 1.5 cc., each, of sow's follicular fluid intracardially during the postestrous period. That the animals were desensitized was shown by the total lack of response of thirteen of these animals to this critical dose of antigen. The remaining two animals in the series died with characteristic symptoms of anaphylactic shock (these two animals had just ovulated).

TABLE 1.—*Gross Shock as Criterion of Hypersensitivity*

Guinea-Pigs	Follicular Fluid or Protein, and Amount, Used in Sensitization	Time Elapsing after Sensitization, Weeks	Critical Dose of Follicular Fluid or Protein	Time of Administration of Critical Dose with Relation to Last Estrus	Comment
7 female	Sow 0.5 cc.	3	Sow 0.5 cc.	Typical anaphylaxis and death
3 male	Sow 0.5 cc.	3	Sow 0.5 cc.	Typical anaphylaxis and death
5 male	Sow 0.5 cc.	3	Cow 0.5 cc.	Typical anaphylaxis and death
2 female	Sow 0.5 cc.	3	Mare 0.5 cc.	Severe shock with recovery
2 male	Sow 1.5 cc.	3	Mare 2.0 cc.	Typical anaphylaxis and death
5 female	Cow 0.5 cc.	3	Cow 0.5 cc.	Typical anaphylaxis and death
5 female	Sow 0.5 cc.	3	Cow 0.5 cc.	Typical anaphylaxis and death
1 female	Cow 0.5 cc.	3	Mare 0.5 cc.	Severe shock with recovery
1 female	Cow 0.5 cc.	3	Ewe 0.5 cc.	Typical anaphylaxis and death
4 male	Cow 2.0 cc.	3	Mare 2.0 cc.	Moderate shock with recovery
1 male	Cow 2.0 cc.	3	Mare 2.0 cc.	Typical anaphylaxis and death
5 male	(Never sensitized)	..	Cow 1.5 cc.	No symptom of shock
5 male	(Never sensitized)	..	Sow 1.5 cc.	No symptoms of shock
10 female	(Never sensitized)	..	Sow 0.5-1.5 cc.	10-16 days after	Death
5 female	(Never sensitized)	..	Sow 0.5-1.5 cc.	10-16 days after	No symptom of shock
15 female	(Never sensitized)	..	Sow 0.5-1.5 cc.	1-10 days after	No symptom of shock
15 female	Sow 0.5 cc.	3	Sow 0.5 cc.	1-5 days after	No symptoms in 13; death in 2
5 male (controls)	Sow 0.5 cc.	3	Sow 0.5 cc.	Typical anaphylaxis with death
A female	1% casein 0.5 cc.	2	0.5% casein 0.5 cc.	7 days after	Slight symptoms with recovery
B female	1% casein 0.5 cc.	2	0.5% casein 0.3 cc.	At estrus	Acute anaphylaxis with death
C female	1% casein 0.5 cc.	2	0.5% casein 0.5 cc.	5 days after	No symptoms
D female	1% casein 0.5 cc.	2	0.5% casein 0.5 cc.	10 days after	No symptoms
E female	1% casein 0.5 cc.	2	0.5% casein 0.3 cc.	At estrus	Acute anaphylaxis with death
F female	1% casein 0.5 cc.	2	0.5% casein 0.15 cc.	1 days after	Slight symptoms

As a control of the antigenicity of the follicular fluid used, five male animals, sensitized three weeks previously to sow's follicular fluid, demonstrated the typical picture of anaphylaxis on intracardial injection of 0.5 cc. of the follicular fluid.

A control series of female guinea-pigs, sensitized to casein, was used to show that this animal is not refractory to anaphylactic shock in general during estrus.

To sum up this section of the work it may be said (1) that the proteins of follicular fluid are antigenic; (2) that the follicular fluids of five mammals thus far studied contain proteins immunologically related, and indeed, as far as determined in this part of the work,

similar; (3) that follicular fluid of the guinea-pig is auto-antigenic, since the primary injection of follicular fluid into female guinea-pigs between the tenth and sixteenth day of the cycle may produce fatal anaphylaxis, and since injection of follicular fluid on the first few days following estrus, into guinea-pigs artificially sensitized to heterologous follicular fluid, elicits no reaction; and (4) that female guinea-pigs sensitized to other proteins are more susceptible to anaphylactic shock during and just following estrus than in diestrus.

THE BRONCHOSPASM REACTION

It was thought advisable to try the Auer and Lewis⁵ bronchospasm reaction on a series of female guinea-pigs sensitized to follicular fluid in order to represent graphically the differences in degree of sensitivity at various stages of the genital cycle. This difference in sensitivity is understood to be due to the interfering factor of the test animal's own follicular fluid.

TABLE 2.—Results of Test for Bronchospasm Reaction in Guinea-Pigs Sensitized to Follicular Fluid

Female Guinea-Pig	Follicular Fluid Used	Date of Sensitization	Date of Reaction	Reaction to Injection of Follicular Fluid		Days After Estrus
				Cow	Sow	
992	Sow	3/ 1/28	3/25/28	(Not given)	Positive	0
12	Sow	3/ 1/28	3/17/28	(Not given)	Negative	1
72	Sow	3/ 1/28	3/17/28	(Not given)	Positive	1
449	Sow	2/13/28	3/31/28	(Not given)	Negative	4
25	Cow	2/ 8/28	3/ 3/28	Semipositive	Not given	6
23	Sow	2/13/28	3/ 3/28	Positive	Not given	12
16	Sow	11/19/28	3/24/28	(Not given)	Positive	14
24	Cow	2/ 8/28	3/ 3/28	Positive	Not given	14
111	Cow	2/ 8/28	3/16/28	(Not given)	Positive	15
22	Sow	2/ 8/28	3/ 3/28	Semipositive	Positive	17

The technic involved in this reaction is essentially that of Koessler and Lewis.⁶ It consists of sectioning the animal's spinal cord at the level of the medulla, inducing artificial respiration at the rate of 20 per minute, and recording such changes in intrathoracic pressure as occur, due to the excursion of the lung, on a revolving drum. In a positive reaction, emphysema occurs immediately, lung excursion is prevented, and the writing lever draws a straight line.

Table 2 is made up from data on experiments with ten female guinea-pigs sensitized to either cow's or sow's follicular fluid. Graphs representative of the various reactions are presented, together with characteristic data. In this series, also, the ovaries (and in most instances, the uteri) of all experimental animals were serially sectioned and histologic correlations made.

5. Auer, J., and Lewis, P. A.: Acute Anaphylactic Death in Guinea-Pigs, *J. A. M. A.* **53**:458, (Aug. 7) 1909.

6. Koessler, K. K., and Lewis, J. H.: Determination of Broncho-Spasm in the Guinea-Pig, *Arch. Int. Med.* **39**:163 (Feb.) 1927.

GUINEA-PIG 449.—Guinea-pig 449, female, was sensitized with 1 cc. of sow's follicular fluid, Feb. 13, 1928. A combined bronchospasm, uterine strip reaction was done, March 31, on the fourth day after estral opening (fig. 1). In this animal, 0.5 cc. and then 1 cc. of sow's follicular fluid injected into the external jugular vein caused no anaphylaxis as shown by the pulmonary reaction as well as by the uterine smooth muscle reaction.

Histologic Observations: The left ovary contained two large, newly formed corpora each of which still contained rather a large amount of colloid in the core. Many follicles in advanced atresia were seen, and the new follicles showed beginning enlargement but very little cavitation as yet. The right ovary was different in having a large, degenerating yellow body and only one corpus. The uterine horns were still swollen but no longer hyperemic.

GUINEA-PIG 23.—Guinea-pig 23, female, was sensitized with 1 cc. of sow's follicular fluid, Feb. 13, 1928. A bronchospasm reaction was carried out, March 3, on the twelfth day after estral opening (fig. 2). On the injection of 1 cc. of cow's follicular fluid into the external jugular vein, a typical bronchospasm was

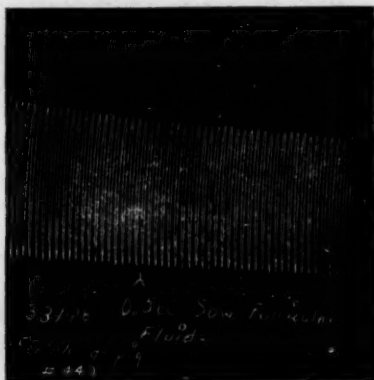


Fig. 1 (guinea-pig 449).—The negative result of the Auer-Lewis operation for bronchospasm reaction following the injection of 1.5 cc. of sow's follicular fluid into the jugular vein on the fourth day post estrus in a female guinea-pig sensitized to sow's follicular fluid.

obtained immediately. On autopsy, the lungs were greatly distended with emphysema, and the uterine horns were in tonic contracture.

Histologic Observations: The left ovary contained about twelve medium-sized follicles all of which appeared healthy, except two; in these, the innermost layer of granulosa cells in some areas showed degeneration. One large corpus showed mitosis of granulosa, as well as of endothelial, cells, and early signs of lutein cell degeneration were seen. The right ovary was essentially similar; it had about fifteen medium-sized developing follicles.

GUINEA-PIG 22.—Guinea-pig 22, female, was sensitized, Feb. 8, 1928, to 0.5 cc. of sow's follicular fluid. A bronchospasm reaction was done, March 3, seventeen days after the last estrous opening (fig. 3). On intrajugular injection of 0.5 cc. of cow's follicular fluid, a semipositive reaction was obtained. Complete bronchospasm occurred when 0.5 cc. of sow's follicular fluid was administered by the same route. The fact that only a semipositive reaction was obtained at this stage

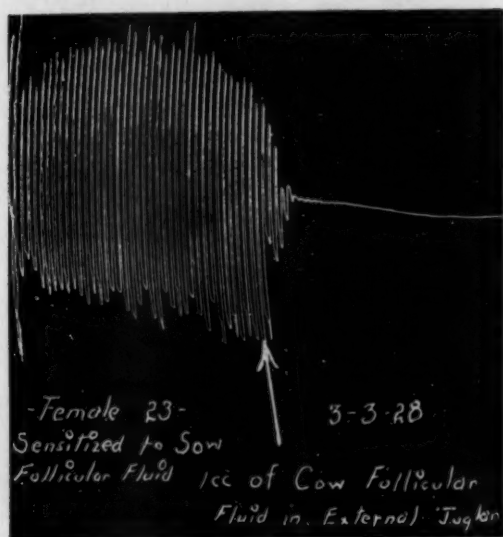


Fig. 2 (guinea-pig 23).—The positive bronchospasm reaction following the injection of 1 cc. of cow's follicular fluid on the twelfth day post estrus in a female guinea-pig sensitized to sow's follicular fluid.

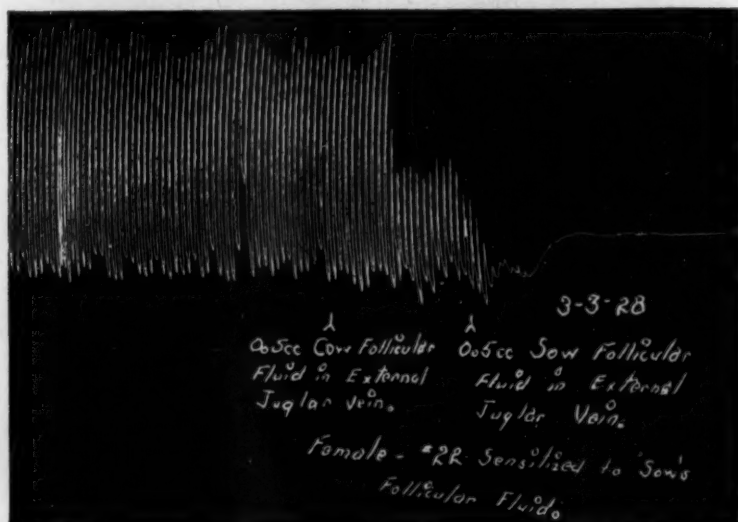


Fig. 3 (guinea-pig 22).—The semipositive bronchospasm reaction to cow's follicular fluid, and the positive reaction to sow's follicular fluid on the seventh day post estrus in a female guinea-pig sensitized to sow's follicular fluid.

of the cycle with heterologous fluid indicates that desensitization was in progress due to the circulation of the animal's own follicular fluid.

Histologic Observations: Each ovary contained more than thirty follicles, most of which were in various stages of atresia, and only one of which would have matured and ruptured. Three corpora in an early stage of degeneration were seen in the left ovary, while the right contained one.

GUINEA-PIG 24.—Guinea-pig 24, female, was sensitized, Feb. 8, 1928, with 0.5 cc. of cow's follicular fluid. A bronchospasm reaction was tried fourteen days after the estral opening (fig. 4). On injection of 3 cc. of a 1:3 solution of cow's follicular fluid in saline solution, which was allowed to run slowly into the external jugular vein, a bronchospasm occurred within four minutes.

Histologic Observations: Each ovary contained more than thirty follicles, the majority of which showed varying degrees of atresia. Two healthy

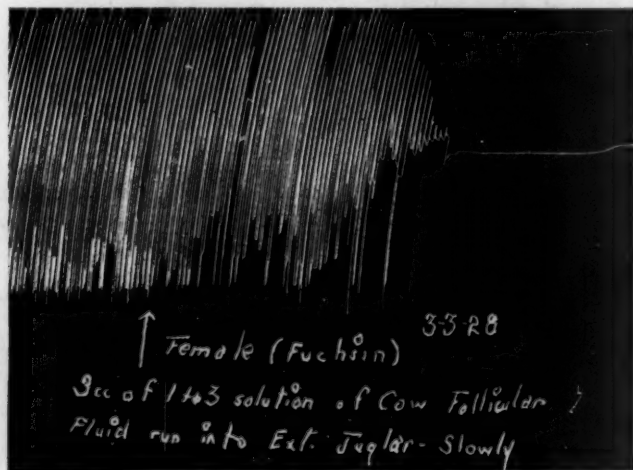


Fig. 4 (guinea-pig 24).—The positive bronchospasm reaction to cow's follicular fluid on the fourteenth day post estrus in a female guinea-pig sensitized to cow's follicular fluid.

follicles were nearly mature. The earliest stage of corpus degeneration was observed in two corpora in this ovary. The endothelial cells seemed to surround degenerating lutein cells.

It developed from this small series of animals that in female guinea-pigs sensitized to foreign follicular fluid an extremely sensitive immunity balance may be readily effected by the test animal's ovarian activity directly referable to the follicular phase. A series of normal female guinea-pigs in which bronchospasm has been produced on primary injection is now being worked with, and it is with these, rather than with artificially sensitized animals, that we hope to explain the finer mechanism governing antigen-antibody balance in the genital cycle.

THE SCHULTZ-DALE REACTION

Attention was next given to the Schultz-Dale⁷ reaction with isolated strips of uterus and gut. It was hoped that in this experiment differentiation might be made immunologically between follicular fluids of different animals.

Ten female guinea-pigs were used in this series, each being sensitized to either sow's or cow's follicular fluid and observed as to its estrous cycle. Like certain animals in the experiments with gross anaphylaxis, some of these animals were found refractive at certain stages of the cycle. This was further evidence of the desensitizing action of the test animal's own follicular fluid, and of the interrela-

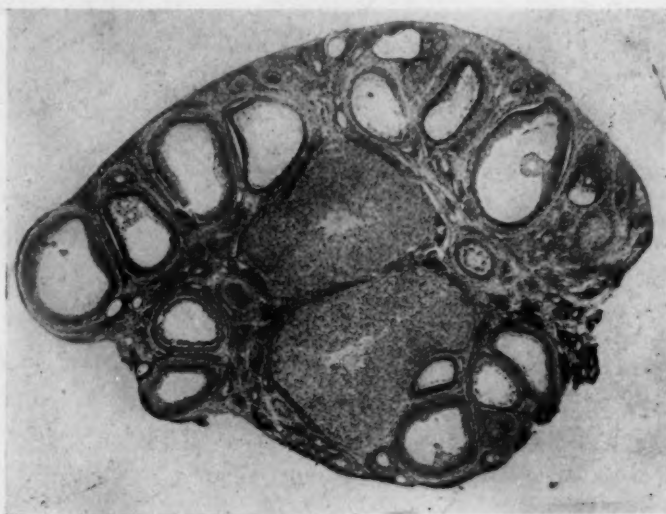


Fig. 5 (guinea-pig 24).—A section of the right ovary.

tionship of the heterologous fluids. It was possible to show that the same degree of sensitivity did not necessarily prevail in both uterine horns, as for example:

GUINEA-PIG 150.—Guinea-pig 150, female, was sensitized to sow's follicular fluid (1 cc. injected intraperitoneally), Feb. 13, 1928. The Schultz-Dale reaction was done February 25, the first day of the cycle (fig. 6, *A*, *B* and *C*).

Dale Reaction: The uterine horns were large and swollen, but not hyperemic. The left uterine horn was refractory to 1 cc. of cow's follicular fluid and to 1 cc. of sow's follicular fluid, but reacted typically to 0.1 cc. of solution of pituitary. The right horn gave no reaction to 1 cc. of cow's follicular fluid, but a typically positive Dale reaction to 1 cc. of sow's follicular fluid. It was relaxed with 0.5 cc. of epinephrine hydrochloride. A strip of gut did not react to cow's but did to sow's follicular fluid. It was relaxed with epinephrine.

7. Schultz, W. H.: Physiological Studies in Anaphylaxis, *J. Pharmacol. & Exper. Therap.* 1:549, 1909-1910.

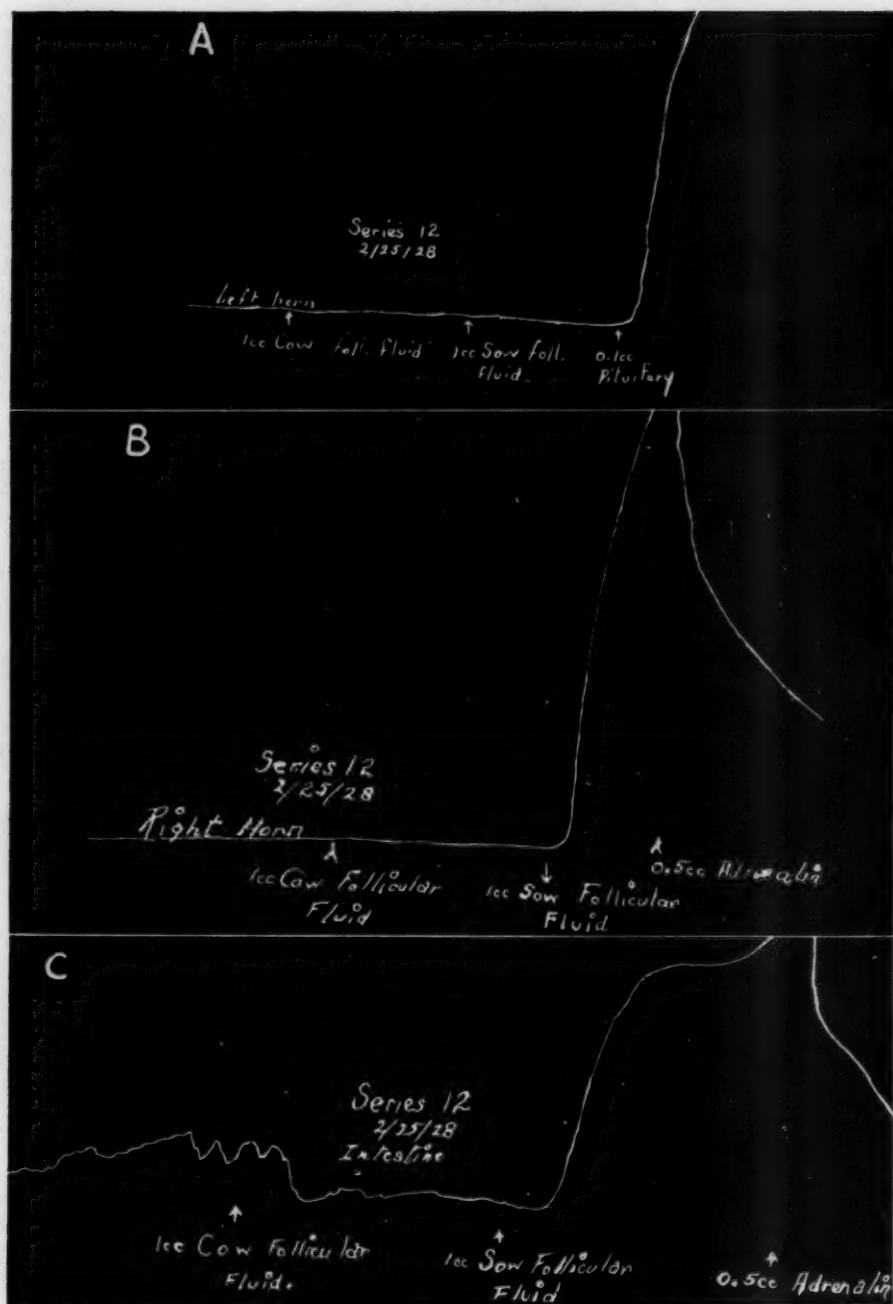


Fig. 6 (guinea-pig 150).—A, the Dale reaction of the left horn of the uterus on the first day of the estrous cycle in a guinea-pig sensitized to sow's follicular fluid: (1) to cow's follicular fluid, (2) to sow's follicular fluid and (3) to pituitrin. B, the Dale reaction of the right horn to (1) and (2). C, the Dale reaction of intestine to (1) and (2).

Histologic Observations: On section, the left ovary was found to be double the right in size. It contained three large ripe follicles bulging with fluid, three degenerating yellow bodies and many follicles in advanced stages of atresia. Figure 7 represents a section through the ovary and shows two prerule follicles and many atretic follicles. The right ovary contains only one yellow body, many atretic follicles and three healthy follicles, not nearly as large as those in the left.

Furthermore, following ovulation, the same degree of sensitivity need not exist in distal and proximal portions of the same uterine horn. To illustrate:

GUINEA-PIG 5²—Guinea-pig 5, female, was sensitized to sow's follicular fluid, Jan. 31, 1928. A Dale reaction was done, February 19, the fourth day of the cycle (fig. 8, *A*, *B* and *C*).

Dale Reaction: On exposure of the uterus of this animal, the right horn was seen to be white, not swollen, and apparently in a resting condition. The distal half of the left horn was as the right, but its proximal half was hyperemic,

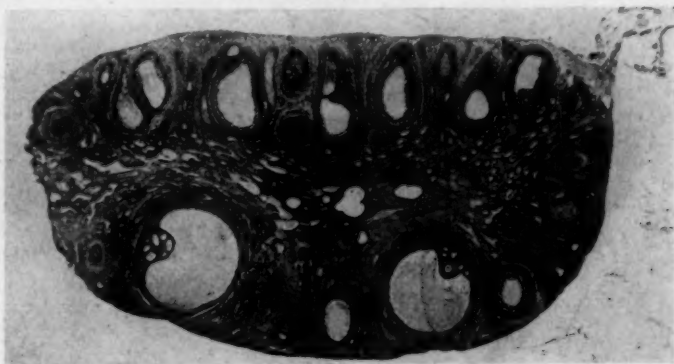


Fig. 7 (guinea-pig 150).—A section of the left ovary.

swollen and apparently still "in reaction." Tracings were accordingly made with the whole right horn, and with the separated distal and proximal halves of the left. As shown in the curves obtained (fig. 8), the right horn did not react to 1 cc. of cow's follicular fluid, but did to 0.5 cc. of sow's follicular fluid. The distal portion of the left horn reacted likewise, but the proximal half was refractive to both cow's and sow's follicular fluid; it did react, however, to pituitrin.

Histologic Observations: The left ovary showed a medium-sized recently formed corpus. Several follicles in advanced stages of atresia were seen, and two medium-sized follicles which had neither ruptured nor degenerated. Two small epithelial-lined cysts were present. The right ovary was essentially the same as the left, except that the new corpus was about half as large.

Positive smooth muscle reactions were readily elicited in both uterine and gut strips with heterologous follicular fluids when the animal's own ovary was in its lutein phase (fig. 9). At this time, apparently, there is no absorption of the soluble substance that later in the cycle desensitizes the animal.

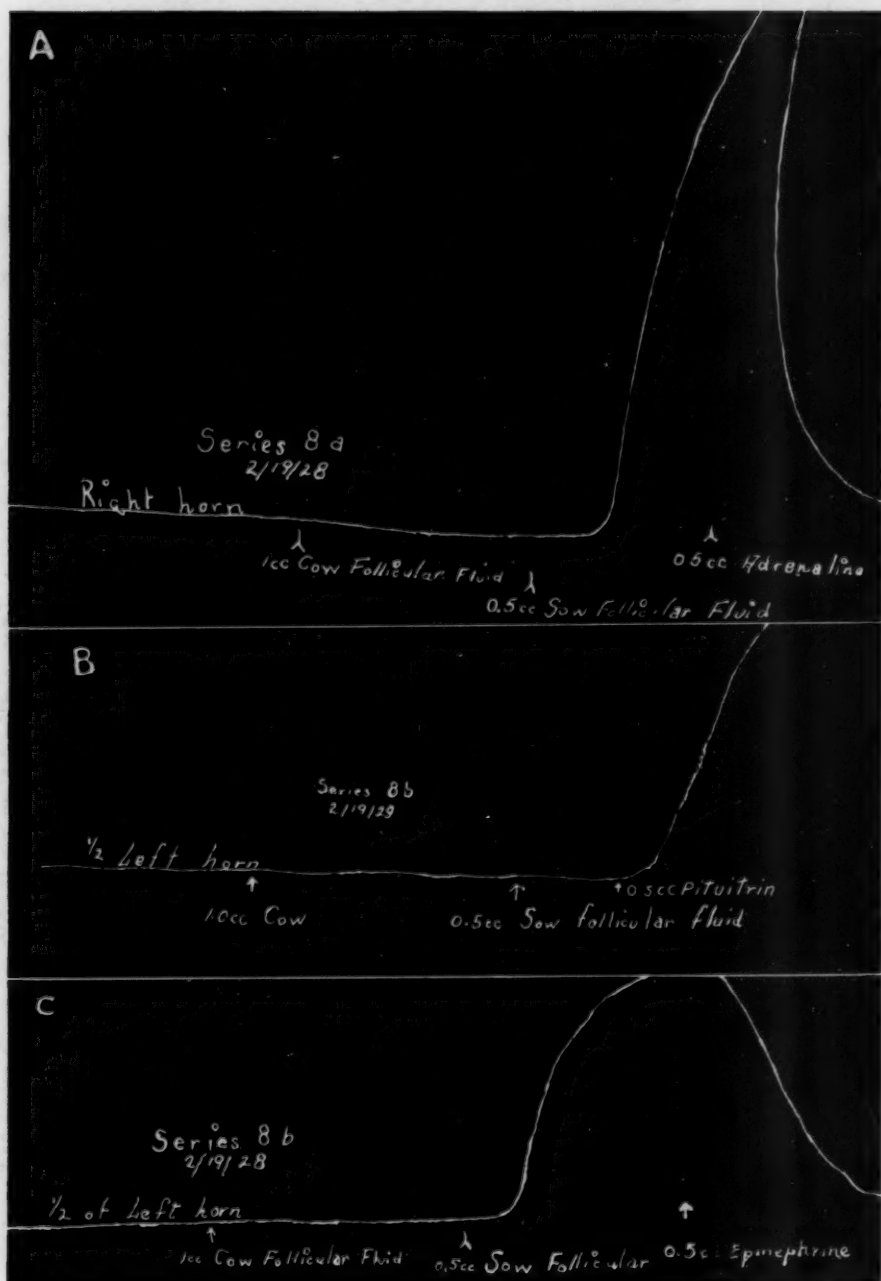


Fig. 8 (guinea-pig 5).—*A*, the Dale reaction of the right horn of the uterus on the fourth day of the estrous cycle in a guinea-pig sensitized to sow's follicular fluid: (1) to cow's follicular fluid and (2) to sow's follicular fluid. *B*, the Dale reaction of the left horn of the uterus, proximal half, to (1) and (2). *C*, the Dale reaction of the distal half to (1) and (2).

After the fourteenth day of the cycle, however, or at the commencement of the follicular phase, it was customary to find the smooth muscle refractive not only to heterologous antigen, but also to the follicular fluid used in sensitization (fig. 10). As did the work with gross

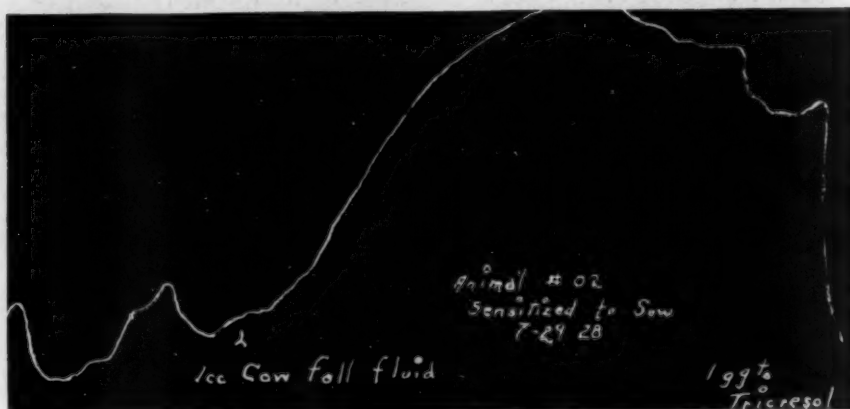


Fig. 9 (guinea-pig 02).—The Dale reaction of the uterus of a sensitized guinea-pig on the fourteenth day of the cycle, when its ovaries were in the lutein phase.

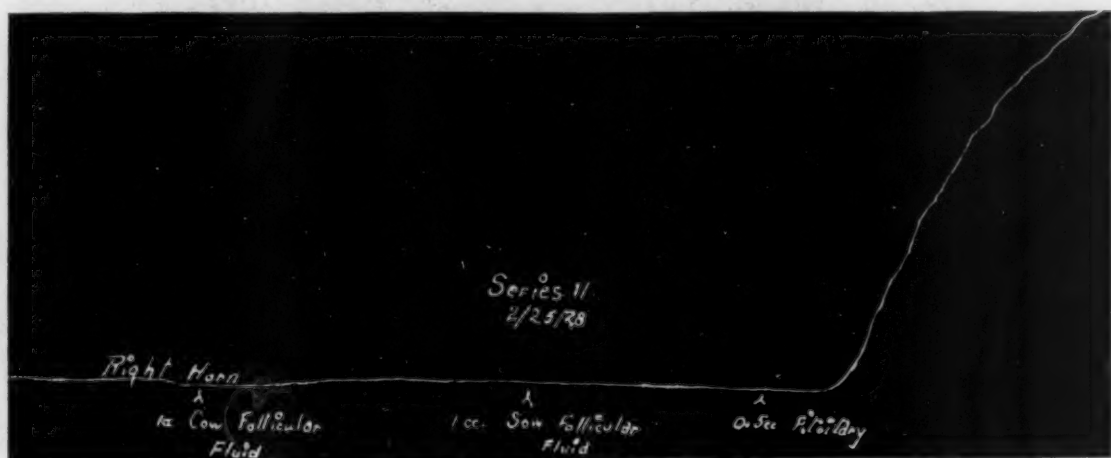


Fig. 10 (guinea-pig 281).—The Dale reaction of the uterus of a sensitized guinea-pig on the sixteenth day of the cycle, when its ovaries were at the commencement of the follicular phase.

anaphylaxis, the work with smooth muscle showed that the test animals' own follicular proteins, or the "specific soluble substances" of the ovary, are apparently responsible for a gradual cyclic desensitization which persists for only a short time.

A series of twelve virgin guinea-pigs, not previously sensitized to heterologous follicular fluid, was then used. It was found possible to elicit typical Dale reactions in the uterus and gut with heterologous follicular fluids at certain stages of the cycle, showing that these animals had become sensitized to their own ovarian proteins (fig. 11).

COMMENT

While this study merely adds another relatively nonspecies-specific antigen to a gradually enlarging list (casein, fibrinogen, crystalline lens, ovoproteins, etc.), we believe that it should be possible to carry this work to a point which may result in the removal of some of the vagueness that accompanies our present conceptions of the functions of the sexual endocrine substances.

It is apparent from the data presented that there is some substance, probably protein in nature, occurring in the various mammalian follicular fluids studied, that is capable of producing the anaphylactic syn-

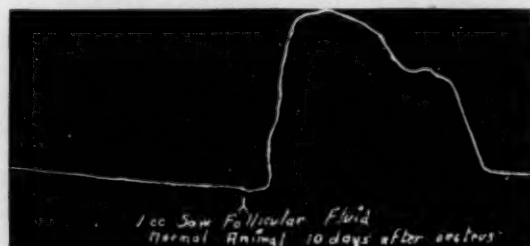


Fig. 11 (guinea-pig 024).—The Dale reaction of the uterus of a normal animal on the tenth day of the cycle.

drome in guinea-pigs. We are unable to state at the present time whether this substance is the same in each of these species, or whether the proteins of these fluids are sufficiently related chemically to give rise to identical immunologic phenomena.

There is, however, no doubt but that these animals are sensitized and desensitized generally during various periods of their sexual cycle by their own follicular fluid. This phenomenon becomes more apparent when local immunization is considered. Following ovulation and liberation of the follicular fluid, both uterine horns, or even part of a horn, may become desensitized, depending on several factors, chief among which are the amount of follicular fluid liberated and in which ovary ovulation occurs. Desensitization may not proceed evenly, so that one horn or even a part may regain sensitivity before the rest of the uterus.

It would appear, however, that a cyclic hypersensitiveness to follicular fluids, as well as to the "rest-substances," is much in evidence in the female guinea-pig. The degree of reactivity of the uterus and

gut seems to be based on an extremely delicate balance between the animal's own follicular fluid and antistances.

While toxicity of ovarian substances has long since been demonstrated, we are not aware that this subject has been given much attention from an immunologic standpoint. Champy and Gley, in 1927, reported that as early as 1912 they had demonstrated what they termed "tachyphylaxie" in female rabbits into which extracts of corpus luteum or whole ovary had been injected. These animals died, and on autopsy showed extreme congestion of the genital organs and the mammary apparatus. We have observed these same phenomena in normal female guinea-pigs on intracardial injection of foreign follicular fluid. Other workers have been more obscure as to the source of the toxic factor. In our work, as high as 5 cc. of sow's, cow's, or mare's follicular fluid, given intracardially, has elicited no toxic symptoms in male guinea-pigs at least 6 weeks old. Animals of both sexes younger than this may show shock on primary injection of as little as 0.5 cc. of these fluids, and this is also true of adult females at a definite stage of the estrus cycle.

SUMMARY

Male guinea-pigs have been used to show by means of gross anaphylactic reactions the relationship of various mammalian follicular fluids. These animals when sensitized to sow's or cow's follicular fluid responded with the typical anaphylactic syndrome on the subsequent injection of sow's, cow's, ewe's, or mare's follicular fluid. None showed ill effects from primary intracardial or intraperitoneal injection of these fluids.

The use of the female guinea-pig introduced a new factor, namely, the effect of the animal's own follicular fluid on the condition of hypersensitivity to heterologous fluids. Our attention was called to this factor, first, by a number of fatalities ensuing on both intraperitoneal and intracardial primary injections into mature female guinea-pigs, of sterile follicular fluid harmless to adult male guinea-pigs; and second, by the fact that female guinea-pigs previously sensitized with impunity to heterologous follicular fluid showed not the slightest symptom of anaphylaxis on reinjection, after the proper interval, provided they had recently ovulated, as determined by the condition of their vaginae.

Knowing that desensitization in the broad sense of the term may be brought about in various ways, and especially by affecting the autonomic nervous system, it was deemed necessary to control this second observation by determining whether just postovulatory nervous state of the guinea-pig was such as to render it refractive to a critical injection of some specific protein to which it was sensitized, other than follicular fluid. Consequently there was included a small series of animals sen-

sitized to casein, which were not refractive to critical injections just following ovulation, but on the contrary more susceptible.

Of a series of fifteen guinea-pigs sensitized to foreign follicular fluid, thirteen are reported refractory to second injection just following estrus. Judging from the histologic observations in the two that suffered shock, one may conclude that ovulation had preceded the critical injection too soon to allow for absorptions of the follicular fluid and general desensitization.

Attention was next turned to animals showing acute shock on primary injection of foreign follicular fluid. It was found that this reaction might be elicited in female guinea-pigs at certain times during the cycle.

By means of the Schultz-Dale technic, it was possible to show that guinea-pigs sensitized to foreign follicular fluids are rendered temporarily desensitized by the elaboration of the animal's own follicular fluid. The same technic shows that normal female guinea-pigs become sensitized to their own follicular fluid at certain times during the estrous cycle.

CONCLUSIONS

The follicular fluids of the four mammals studied (sow, cow, mare, ewe) are closely related immunologically; they are similarly related to the follicular fluid of the experimental animal, the guinea-pig.

Guinea-pig follicular fluid is auto-antigenic.

Guinea-pigs artificially sensitized to follicular fluid proteins are temporarily desensitized by the liberation of their own follicular fluid.

Fatal anaphylaxis may be produced at a definite time, in normal guinea-pigs, on primary injection of heterologous follicular fluid.

PRIMARY CARCINOMA OF THE URETER

REPORT OF A CASE AND REVIEW OF THE
LITERATURE *

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REPORT OF CASE

History.—Mrs. F. L., white, aged 59, complained of blood in the urine. It had been present for a week before examination. Her familial history and her past history were unimportant. The results of physical examination were negative. A slight secondary anemia was present. The Wassermann reaction of the blood was negative. Repeated examination of the urine showed the presence of a trace of albumin with red blood cells and leukocytes microscopically. Ureteropyelograms showed ptosis of the right kidney with irregularity in filling, dilatation and kinking of the right ureter. The filling defect, 1.5 cm. below the lower border of the ileum, according to the roentgenologic report of Dr. Amedee Granger, was most probably the result of a new growth. Reexamination resulted in similar observations and conclusions.

Under spinal anesthesia, ureterectomy was performed by Drs. Lindner, Ochsner and Maihles. Forty days later, right nephrectomy was performed. Recovery after both procedures was uneventful.

Gross Observations in Ureter.—The specimen was a portion of the ureter measuring 7.5 cm. in length. Near one end was a fusiform dilatation (fig. 1) 4 cm. in length and 0.5 cm. in its largest diameter. Above and below this dilatation, the ureteral wall was thin and elastic, presenting no gross changes externally. At the site of the enlargement, the ureteral wall was considerably thickened, nonelastic and firm. When the ureter was opened, a tumor was found impinging on and practically occluding its lumen, at the site of the externally noted enlargement (fig. 2). The tumor was attached to the ureteral mucosa by a broad base and presented numerous, dense, papillalike projections varying in size from hairlike strands to strands from 2 to 20 mm. thick. These papillary projections were densely compact, some of the larger ones showing at their free ends cauliflower-like protuberances. At the periphery of the growth, some of the smaller papillae could be removed by plucking. After such removal, the ureteral wall revealed a pitted and roughened reddish-brown surface. For the most part, however, removal by plucking was not possible, the papillary projections being firmly adherent and apparently a part of the ureteral mucosa.

Microscopic Observations in Ureter.—Cross-sections of the tumor mass showed papillae composed of epithelial cells and separated by thin layers of vascular connective tissue. Here and there adjacent papillae showed fusion of epithelial elements with the formation of solid sheets of cells. The individual epithelial cells were densely packed, mostly large and irregular in shape, though generally polyhedral; many showed pyknotic nuclei. Mitotic figures were noted. For the most part, the wall of the ureter was not penetrated, but here and there aggregates of irregularly shaped, intensely staining epithelial cells were noted invading the

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* From the Department of Pathology of the Charity Hospital.

various layers of the ureter, especially the submucosa. Some such aggregates were surrounded by round cells. At the bases of many papillae, cell polarity was lost.

Gross Observations in Kidney.—The specimen was a kidney opened through the pelvis by an incision in the longitudinal diameter of the organ. It weighed 95 Gm. and was rather flabby. The external surfaces varied from brownish red to grayish red and were rather smooth, moist and glistening, with small petechial hemorrhages appearing through the capsule. In the region of the pelvis there was some fat. The capsule stripped with some difficulty, revealing a rather granular surface varying from brownish red to grayish red, the darker areas

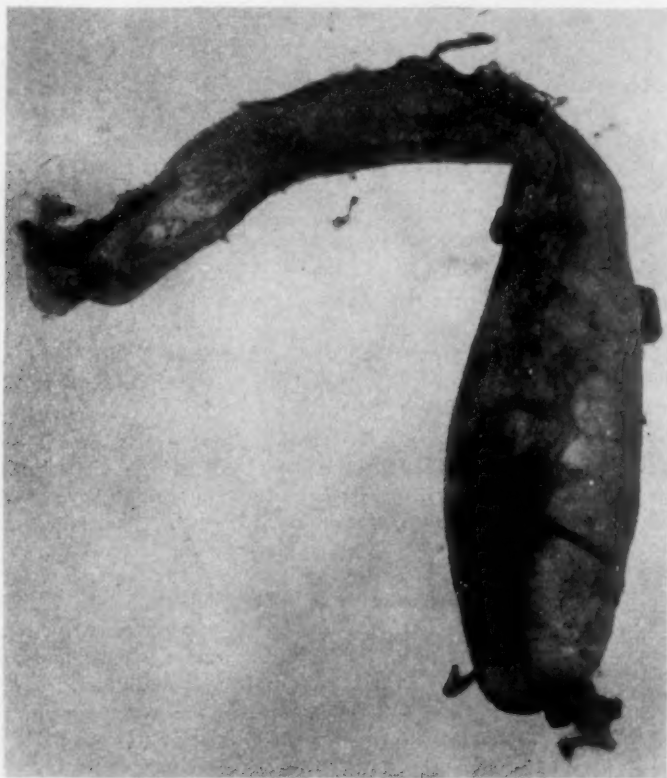


Fig. 1.—External appearance of a tumor-containing ureter.

evidently representing capillary hemorrhages. The internal surfaces revealed by sectioning varied from grayish pink to grayish brown and showed obliteration of normal markings, with an extremely thin and flat cortex wherever discernible. The pelvis was rather dilated and irregularly shaped, its mucosa being granular and presenting throughout minute petechial hemorrhages. Such small hemorrhages were also noted throughout the organ. Careful sectioning failed to reveal any new growth or stone formation.

Microscopic Observations in Kidney.—Microscopic study of numerous sections of the kidney showed generally the same changes. All the blood vessels were thickened and engorged. The tubular and glomerular lining cells were generally the seat of cloudy swelling and fatty metamorphoses. Most of the glomeruli were

small and adherent to their capsules and lay close together. Many presented degenerative changes, some having undergone marked hyalinization; some few, however, were evidently undergoing hypertrophic compensatory changes. Numerous atrophic tubules were seen. A highly cellular connective tissue stroma was noted, containing inflammatory elements.

REVIEW OF THE LITERATURE

Reports of primary carcinoma of the ureter have appeared in medical literature since 1879. Hektoen,¹ in reporting a case in 1896, referred to two earlier ones. Albaran, in a review of the literature of

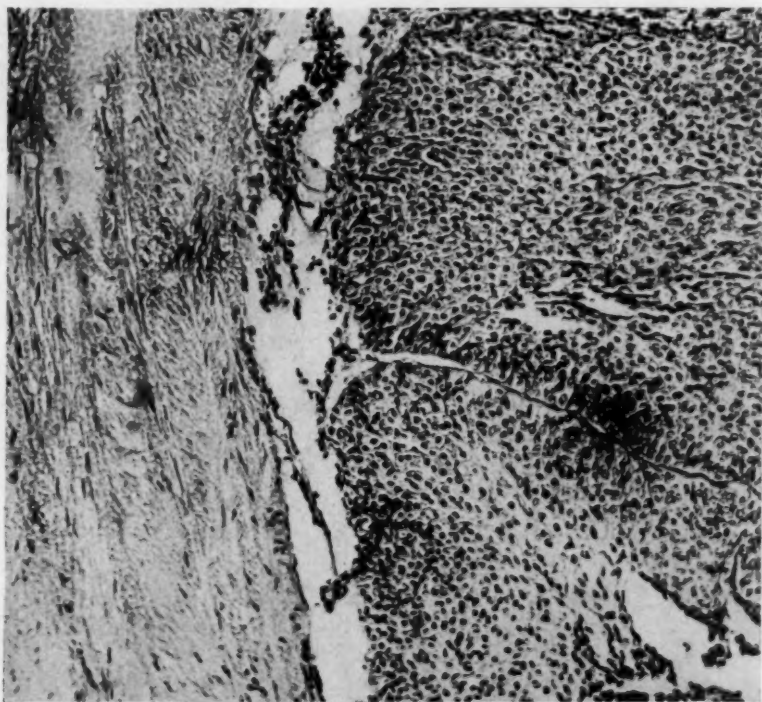


Fig. 2.—Low power photomicrograph showing early invasion of ureteral wall with loss of basal cell polarity.

primary ureteral tumors in 1902, compiled 10 case reports, of which five dealt with carcinomatous, two with papillary and three with non-papillary growths. Richter² in 1909 reviewed the literature of primary carcinoma of the ureter and found eleven reports of cases. Butler,³ in

1. Hektoen, L.: Primary Carcinoma of the Ureter, *J. A. M. A.* **26**:1115 (June 6) 1896.

2. Richter, T.: Primäres Carcinom des rechten Ureters, *Ztschr. f. Urol.* **3**:416, 1909.

3. Butler, F. A.: A Case of Primary Carcinoma of the Ureter, *Clifton M. Bull.* **2**:48, 1914.

1914, found nineteen previous reports of cases. Judd and Struthers,⁴ in 1921, found twenty-five and added their own. McCarthy and Meeker,⁵ in 1923, in the last complete review published, added a number overlooked in previous summaries, which, together with their own, brought the total to thirty-three. We have been able in a thorough search to find a total of forty-seven reports of cases, including a few overlooked in previous reviews. These, together with the report we have now

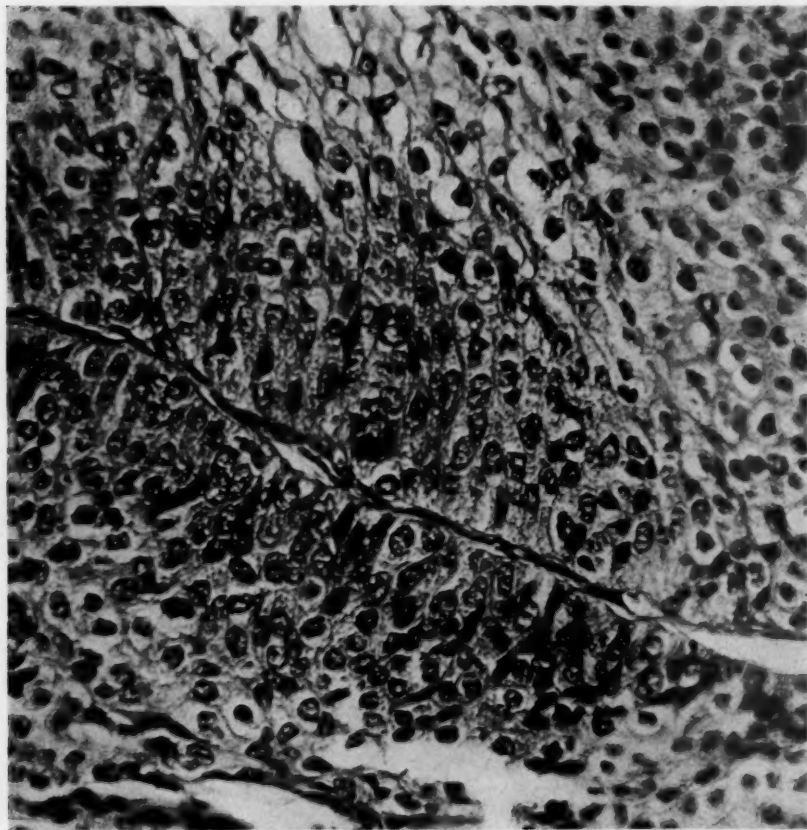


Fig. 3.—High power photomicrograph showing cell polymorphism, pyknosis, some mitosis and beginning fusion of cell elements.

recorded, bring the total number of reports of primary carcinomas of the ureter to forty-eight. The salient features of these reported cases are tabulated in table 1.

4. Judd, E. S., and Struthers, J. E.: Primary Carcinoma of the Ureter, *J. Urol.* **6**:115, 1921.

5. McCarthy, J. F., and Meeker, L. H.: Primary Carcinoma of the Ureter, Report of a Case and Review of the Literature, *J. A. M. A.* **81**:104 (July 14) 1923.

In critically reviewing the various reports, much difficulty was encountered in the histologic classification of the tumors, owing principally to the varying and at times bizarre nomenclatures adopted by the authors. We have therefore classified them, for the most part, on the basis of their papillary or nonpapillary character. Again, the title of a report would indicate that the tumor under consideration was malignant, but the body of the article and the histologic description of the growth, when given, made its classification as malignant dubious. Therefore, with the exception of Kleinschmidt's⁶ case, we have not included any case in the report of which the author does not clearly state that there was enough histologic evidence to classify the tumor as malignant or in which the histologic description of the tumor or the mechanical reproduction of sections thereof does not make its classification as malignant apparent. The exception in Kleinschmidt's case is made because of Kümmel's⁷ statement that repeated histologic examinations of the growth revealed it to be an early type of malignant tumor. On this basis, we have been obliged to exclude such tumors as Takahashi's,⁸ Dózsa's⁹ case III and Cassuto's.¹⁰ Histologic study of these tumors, especially of the latter's, in view of its apparent recurrence and extension, may possibly have revealed malignancy. However, as no record of such examinations occurs in the reports, the tumors these observers encountered must be regarded as, at most, suspicious growths primarily either of the ureter or of the kidney pelvis and ureter, and cannot with justification be included in this summary of proved primary carcinomas of the ureter.

Incidence with Regard to Age and Sex.—Of the forty-eight ureteral tumors reported, twenty-five occurred in males; twenty-three in females (table 2). The earliest age at which a case occurred in men was that of 35 years; two cases are on record. In women, the earliest age at which a case occurred was that of 36. The oldest age at which a case occurred in men was that of 74; in women, that of 89. The greatest number of cases (fourteen) in both sexes occurred in persons between the 60th and the 70th years. In men, the greatest occurrence for any decade was that between the 60th and the 70th years (eight cases); in

6. Kleinschmidt, R.: Beitrag zur Kenntnis der primären Uretertumoren, Deutsche Ztschr. f. Chir. **191**:103, 1925.

7. Kümmel, H.: Ueber Nierenbecken und Uretergeschwülste, Monatschr. f. Harnkrankh. u. sex. Hyg. **2**:195, 1928.

8. Takahashi, A.: Kasuistische Mitteilung der merkwürdigen Uretergeschwülste die bei der cystoskopischen Untersuchung beobachtet wurden, Ztschr. f. urol. Chir. **22**:172, 1927.

9. Dózsa, E.: Weitere Beiträge zur Kenntniss Zottengeschwülste des Nierenbeckens und Ureters, Ztschr. f. urol. Chir. **22**:81, 1927.

10. Cassuto, A.: Uro-pyonéphrose due à un papillome implanté sur le méat urétéral, Lyon chir. **24**:253, 1927.

TABLE 1.—Data in 48 Recorded Cases of Primary Carcinoma of the Ureter

Author, Year	Age of Patient	Sex	Location of Carcinoma	Histologic Classification	Extension by		Duration
					Continuity	Metastases	
Wiesing and Blx: Hygeia 40: 468, 1879	41	F	Right upper third	Nonpapillary	Peritoneum, perirectal glands	Some time
Davy ^{1a}	53	M	Left lower third	Nonpapillary	Rectum, bladder	Liver	2 years
Jona: Centralbl. f. allg. Path. u. Anat. 5: 659, 1894	43	F	Left lower third	Papillary
Voelcker: Tr. Path. Soc. London 46: 133, 1895	68	M	Left lower third	Papillary	Peri-ureteral	Liver, retro-peritoneal glands, lungs	1 year
Rundle ¹¹	46	M	Right lower third	Squamous cell	Seminal vesicles	Liver lungs
Hektoen ¹	50	F	Right lower third	Non-papillary	Ileum, peri-ureteral	8 months
Toupet and Guenoit: Bull. Soc. anat. de Paris 73: 678, 1898	89	F	Left diffuse	Papillary
Minieh: Pest. med.-chir Presse 24: 911, 1902	66	F	Right lower third	Squamous cell	Vagina, bladder
Gerstein: Inaug. Diss., Kiel, 1902	67	M	Right lower third	Nonpapillary	Bladder	Lungs kidney	9 months
St. Thomas. Hosp. 32: 26, 1903	60	M	Left lower third	Papillary	Perivertebral glands to diaphragm	6 months
Adler, Monatschr. f. urol. 10: 129 1905	69	M	Left lower third	Papillary cornifying	4th lumbar vertebra	8 weeks
Metcalf and Safford ¹⁴ ..	47	M	Left lower third	Nonpapillary	Sacrum	Kidney	Years
Vorpahl ²⁵	60	F	Right lower third	Nonpapillary, squamous cell	Liver, lungs	1 year
Zironi ¹⁴	36	F	Right lower third	Squamous cell	7 months
Richter ²	80	F	Right lower third	Papillary	Adjacent glands	3 months
Paschkis: Wien. klin. Wchnschr. 23: 361, 1910	65	M	Left lower third	Papillary	Periureteral	Adjacent glands	4 months
Israel and Lowenstein: Berl. klin. Wchnschr. 47: 2381, 1910	56	F	Left multiple	Papillary	Spleen glands	10 years
Chevassu and Mock: Bull. et mém. Soc. Nat. de chir. 38: 522, 1912	53	M	Left middle	Papillary	5 weeks
Chiari: Ztschr. f. urol. 18: 672 1914	54	F	Left middle	Papillary	3 months
Butler ²	53	M	Right middle	Squamous cell	Peri-ureteral	19 months
Schmitt: J. Cancer Research 1: 461, 1916	55	F	Left upper third	Nonpapillary	Vertebra: 11 dorsal, 3 lumbar	Liver	9 months
Spiess ²⁴	41	F	Right lower third	Nonpapillary	About ureteral orifice	Lungs, glands	9 weeks

TABLE 1.—Data in 48 Recorded Cases of Primary Carcinoma of the Ureter—Continued

Author, Year	Age of Patient	Sex	Location of Carcinoma	Histologic Classification	Extension by		Duration
					Continuity	Metastases	
Finsterer: Wien. klin. Wchnschr. 28: 81, 1927	35	M	Left lower third	Papillary	Papillary growths		4 years
Van Capellen: Beitr. z. klin. Chir. 40: 138, 1916	46	F	Right middle	Papillary			14 years
Hofmann: Ztschr. f. urol. 15: 369, 1916	35	M	Left lower third	Papillary (early)	Bladder		4 years
Knack: Deutsche med. Wchnschr. 44: 982, 1918	73	M	Left middle and lower third	Papillary	Bladder		
Quinby: J. Urol. 4: 439, 1920	40	F	Left middle	Nonpapillary	Periureteral		3 weeks
Rathbun, Internat. J. Surg. 6: 232, 1920	40	M	Left middle	Papillary			2 years
Walker ²⁷	38	M	Right entire	Papillary	Periureteral	Liver, abdomen	6 years
Judd and Struthers ⁴ ...	48	M	Left lower third	Papillary			2 years
Suter: Ztschr. f. urol. Chir. 10: 522, 1922	63	M	Left lower third	Nonpapillary	Periureteral		10 months
Idem.	64	F	Right lower third	Nonpapillary			2½ years
Aechner: Surg. Gynec. Obst. 35: 749, 1922	38	M	Right upper third	Squamous cell			9 months
Meeker and McCarthy ⁵	49	M	Right entire	Papillary		General: liver, lungs, glands, etc.	6 months
Kraft ²¹	52	F	Left middle and lower third	Papillary (early)			4 months
Crane and Knickerbocker: J. A. M. A. 82: 1930 (June 14) 1924	42	F	Right lower third	Nonpapillary			
Kretschmer: Surg. Gynec. Obst. 38: 47, 1924	74	M	Right lower third	Nonpapillary		Carcinoma of lip 20 years previously	5 weeks
Papin: J. d'urol. 17: 4, 1924	57	M	Right upper third	Nonpapillary			2 months
Marz: J. Urol. 12: 49, 1924	60	F	Right lower third	Nonpapillary	Had been operated on for carcinoma of uterus 10 years before		5 months
Morse, H. D.: J. Canadian M. A. 15: 402, 1925	54	M	Right lower third	Papillary			1 year
Kleinschmidt ⁶	65	M	Right lower third	Papillary			8 days
Stewart ¹⁷	75	F	Right upper third	Papillary			8 months
Posner: Geburtsch. u. Gynäk. 75: 86, 1926	66	F	Right lower third	Papillary			8 months
Glas ²³	71	F	Right lower third	Nonpapillary	Periureteral and wall of opposite ureter		10 weeks
Viethe: Ztschr. f. urol. 21: 605, 1927	45	M	Left middle	Papillary			Several years
Hunt: S. Clin. No. Amer. 7: 1464, 1927	67	M	Right lower half	Papillary			1 year
Player ²²	65	F	Left upper third	Papillary	Periureteral		
Authors' case	59	F	Right lower third	Papillary			1 week

women, that between the 50th and the 60th years (six cases) and that between the 60th and the 70th years (six cases).

Sites of Tumors.—Twenty-six tumors were of the right ureter, twenty-two of the left (table 3). The largest number occurred in the lower third of the ureter, eighteen such tumors occurring in the right and eleven in the left ureter. The upper third of the ureter was less frequently involved; four times on the right side and twice on the left.

Types of Tumors.—Twenty-eight of the tumors were of frank papillary type and were so designated in the reports. The remaining were classified as nonpapillary or, at least, their papillary features were not prominent. For these, such designations as "medullary," "epithelial," "transitional celled," "carcinoma simplex," "tubular," "adenomatous," "squamous," "mucous membrane carcinoma," "cylindric," "encephaloid," "keratoid" are encountered. We have not found it pos-

TABLE 2.—Incidence of Primary Carcinoma of the Ureter with Regard to Age and Sex

	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	Total
Male.....	4	6	5	8	2	0	25
Female.....	1	6	6	6	2	2	23

TABLE 3.—Sites of the Occurrence of the Tumors

	Upper Third	Middle Third	Lower Third	Diffuse or Multiple	Total
Right ureter.....	4	2	18	2	26
Left ureter.....	2	5	11	4	22

sible to classify the growths, except as regards their papillary characteristics in general.

Etiology.—The etiology of ureteral tumors is unknown, although many theories attempting to account for their occurrence have been advanced. Of these, the following deserve mention:

1. Leukoplakia, with an acceptance of leukoplakia as a process primarily and essentially malignant.
2. Leukoplakia with intervening malignant metamorphosis.
3. An ascending epidermization.
4. Cell inclusions or enclavements occurring during embryonal development and in adult life.
5. Mechanical irritation.
6. Chronic inflammatory irritation.
7. So-called benign hyperplasia of the mucous membrane (diffuse papillomatosis, discrete papilloma formation).

Most German authors lay great stress on leukoplakia, so often encountered in the renal pelvis and ureters, either considering the leukoplakia itself as a malignant or premalignant manifestation or assuming that it is capable of an intervening malignant metamorphosis. Some even assume a predisposition of the tissues of the entire urinary tract to pathologic growths. That this leukoplakia so often stressed as etiologically important is not extremely important so far as primary ureteral tumor is concerned, is suggested by the fact that the ureter alone is rarely involved in leukoplakic processes, there being generally a concurrent involvement of the renal pelvis and bladder. However, leukoplakia when involving the ureter has been encountered only unilaterally; no case of frank bilateral primary ureteral malignancy is recorded, although numerous cases of tumor of the bladder and renal pelvis with coexistent ureteral tumor have occurred.

Tumors of frank ectodermal origin, such as were first described by Rundle¹¹ and since by many others, are possibly best explained on the basis of developmental abnormalities, although the interesting and to some extent enticing theory of metaplasia must be considered in accounting for them. When one considers that after the formation of the mesoblastic pronephron the ectodermal cloaca comes in contact with and invaginates into it, one can satisfactorily account for the accidental carrying of displaced ectodermal cells to various parts of the urinary tract, with subsequent development of such cell nests or enclavements into tumors as a result of factors and processes at present not understood. This may be satisfying in showing the sites at which such tumors may occur, but certainly this little satisfies one as to the all important questions as to how and why the tumors occur even in such cell displacements.

Distinct from this concept of development in cell nests produced as the result of embryonal abnormalities is the suggestion of many authorities that the so-called islands of Brunn are the points of departure for neoplastic processes in the ureter. These, as is well known, consist of epithelium reaching downward from the mucous membrane and giving rise to isolated aggregates of epithelial cells below the covering epithelium. To some, these islands must be considered as the expression of an inclination to proliferation normally possessed by the mucosa of the ureter, this inclination seemingly increasing with age and with the presence of chronic inflammatory processes. Undoubtedly, the observations of Harbitz¹² and Boccolari¹³ indicate that this liability of the

11. Rundle, H.: Epithelioma of Ureter Causing Hydronephrosis, *Tr. Path. Soc. London* **42**:128, 1896.

12. Harbitz, F.: Ureteritis cystica, *Norsk. Mag. f. M. Sc.* **71**:126, 1918.

13. Boccolari, Segolini A.: Ureterite cistica e fibro-papilloma cistico dell'ureter in bovini, *Gior. di med. vet. Torino* **77**:132 and 161, 1928.

mucous membrane of the ureter to form epithelial islands may result in either cyst or tumor formations, again through factors and by processes not fully understood.

Mechanical irritation playing, as it does at times, such an important rôle in the production of tumors, the ureteral neoplasm might be expected frequently to exist as a concomitant of calculus formation. Such, however, is not the case, though Zironi¹⁴ and Metcalf and Safford,¹⁵ among others, have inclined to the view that there is an etiologic relationship between calculi and neoplasms of the ureter. In only six of the forty-eight cases have calculi been present. Undoubtedly, as in Metcalf and Safford's and Davy's¹⁶ cases, for example, the constant irritation caused by an impacted calculus must be considered as an important predisposing factor. However, as Stewart¹⁷ pointed out, and as is well exemplified in Le Dentu's¹⁸ case, though this was one of a benign tumor, the concretions may develop subsequently to the ureteral obstruction and urinary decomposition occasioned by the tumor. Again, tumor cells themselves may act as nuclei for the production of stones. Most of the cases of tumor with coincident lithiasis were cases of squamous, usually cornified, epithelial neoplasms of the upper urinary tract and not of the lower tract. That other irritants can possibly cause tumor formation must be admitted, especially in view of Leone's¹⁹ experimental demonstration thereof with tar.

That the so-called papillomas so often encountered in the renal pelvis, ureter and bladder play an important part in the development of carcinoma cannot, in view of present knowledge, be denied. The consensus at present seems to favor their being essentially tumors and not, as they were previously considered, hyperplasias of the mucous membrane. It is undeniable that many cases which after microscopic study have been diagnosed as simple, benign papillomas of the renal pelvis, ureter or bladder have subsequently developed as cases of carcinoma. Again, undoubted carcinoma has been found in the renal pelvis with typical benign papilloma in the ureter as well as in the kidney pelvis. It is such histologic and clinical considerations that have recently led so many authorities, Kümmel included, to take the

14. Zironi, G.: Cancer primitif de l'uretère droit, *Ann. d. mal. d. org. gen.-urin.* **27**:81, 1909.

15. Metcalf, W. F., and Safford, H. E.: A Case of Carcinoma of the Ureter, *Am. J. M. Sc.* **129**:50, 1905.

16. Davy, R.: Clinical Lecture on Excision of Left Kidney, *Brit. M. J.* **2**:757, 1884.

17. Stewart, R. L.: Primary Tumors of the Ureter, *Brit. J. Surg.* **13**:667, 1925-1926.

18. Le Dentu, A.: *Ann. d. mal. d. org. gen.-urin.* **17**:955, 1899.

19. Leone, P.: Tumori sperimentali del rene e dell'uretère da catrame, *Arch. ed. atti. Soc. ital. di chir.* **34**:111, 1927-1928.

rather radical point of view that every papillary proliferation of the mucous membrane of the renal pelvis or of the ureter is a malignant tumor. Undoubtedly, this point of view is the safest so far as the future of the patient is concerned.

Pathology.—A survey of the histology in the cases of primary ureteral tumors reported suggests the following simple classification:

Epithelial tumors

Simple or benign papilloma

Malignant papilloma (papillary carcinoma or papillary epithelioma)

Nonpapillary carcinoma or epithelioma (simple, squamous, adenomatous)

Connective tissue tumors

Sarcoma

Myosarcoma

Simple or Benign Papilloma: The type of ureteral tumor most frequently met with by far is that of the simple or benign papilloma. It may occur singly, as groups of multiple tumors or as a generalized papillomatosis affecting much of the ureter. It possibly shows a predilection for either the upper or the lower end of the organ, and occasionally occurs at each extremity, as in Le Dentu's case. It may be sessile or pedunculated, at times markedly so, as in Culver's²⁰ case in which the tumor consisted of a mass 3 cm. long attached to the ureteral mucosa by a narrow pedicle. Occurring in the lower portion of the ureter, it may extrude through the ureteric orifice, as noted by Kraft²¹ and others.

Histologically, the ureteral papilloma is no different from that encountered in the bladder or renal pelvis. Essentially, it consists of branching, poorly cellular, vascular, connective tissue cores or stalks surmounted by multiple layers of well differentiated epithelial cells occurring in a variable number of layers, the whole giving rise to a villous or papilla-like arrangement. The individual epithelial cells are rather uniform in size, regular, symmetrical and usually attached at right angles to the cellular stalk. The cells do not appear to infiltrate the connective tissue stalk at their points of origin, but here and there aggregates of small round cells, probably a manifestation of irritation, may be noted. Whether broad-based or pedunculated, the tumor shows no tendency to infiltration or invasion at the point of attachment.

Malignant Papilloma: This group comprises those tumors classified as papillary carcinoma and papillary epithelioma, and includes neoplasms of varying degrees of malignancy. Almost invariably, the malignant papilloma occurs singly and appears to have a predilection for the lower

20. Culver, H.: Papilloma of the Ureter, *J. Urol.* 6:331, 1921.

21. Kraft, S.: Primary and Secondary Ureteral Papillomas, *Ztschr. f. urol. Chir.* 16:385, 1922.

part of the ureter. Macroscopically, it differs but little from the so-called benign papilloma. Microscopically, it may manifest varying stigmas of malignancy with a gradual transition from nonmalignant to malignant features such as to necessitate the most careful histologic study for accurate diagnosis, as emphasized by Richter, Kümmel, Glas²² and others. In some cases, only early signs of local malignancy, such as increased proliferation of slightly atypical cells with a loss of basal cell polarity, are noted. In others, there is much infiltration at the point of attachment, even to such an extent as to be observable macroscopically. The individual cells in the more malignant types are heaped up in thick layers, many showing marked polymorphism with large and small cells occurring in disorderly, disarranged masses. Most important is the tendency of these cells to infiltrate at their points of origin the stalks or cores or the connective tissue substance of the stalks. Mitosis in varying degrees is usually prominent. Destructive infiltration of the ureteral wall and invasion of periureteral tissue occurs in the pronouncedly malignant types.

Nonpapillary carcinoma: This group comprises the more uncommon forms of epithelial tumors of the ureter such as those classified variously and at times bizarrely as "medullary," "encephaloid," "columnar," "adenomatous," "cylindric," "transitional celled," etc. In this group may be placed the squamous cell tumors and tumors of frank ectodermal derivation. Generally speaking, ureteral tumors of this group are the most malignant and show the earliest and most extensive metastasis. Histologically, their recognition is comparatively simple, the stigmas of malignancy being unmistakable and papillary or villous formation being absent or at best simply suggested in the general arrangement of the tumor masses. That at least some of the morphologic and histologic characters presented by these tumors may originate from simple papillomas seems proved by Leone's experimental demonstration of the progressive evolution of neoplastic epithelial processes from simple papillomas to squamous cell, papillary and even alveolar carcinomas.

Connective Tissue Tumors: These tumors, of no special interest in this report, but mentioned for the sake of completeness, are extremely rare. Stewart and Kümmel agreed that only five have been reported. One, Ribbert's case, is classed as a myosarcoma. cursory examination of the reports leads us to believe that in most of the cases, possibly all, the ureter was only secondarily invaded by the sarcomatous growth.

Malignancy and Metastasis.—As previously indicated, there is much confusion regarding the exact position that must be assigned to the so-called benign papillomas of the urinary tract as regards malignancy.

22. Glas, R.: Primary and Metastatic Cancer of Ureter, *Wien. klin. Wchnschr.* 39:1145, 1926.

The consensus of latter day investigators, as stressed especially by Dózsa, appears to be that benign papillomas of the urinary tract, if such there are, are extremely rare and that in most, if not all, such tumors careful histologic examination will show malignancy, although at times early. Undoubtedly, the clinical course of most of the tumors diagnosed as simple papillomatous tumors supports this view, extreme though it may appear. Glas and Player²³ asserted and emphasized that the metastasis from a so-called simple papilloma may exhibit all the signs of malignancy. Janssen,²⁴ among others, believed that papillomas of the urinary tract do not extend until lesions of the mucosa, inflicted by instrumentation or otherwise occur. This view of extension of the so-called simple papillomas by engrafting is rather fully expressed by many authors and certainly is strongly suggested by such cases as Vorpahl's,²⁵ Spiess²⁶ and Walker's,²⁷ among others. Some authorities assert that in contradistinction, the most malignant and especially the nonpapillary types of tumor extend by means of the lymphatics. A summary of the pathologic observations in the reported cases does not give much information concerning metastasis, and the assumption of a lymphatic route for metastasis, while undoubtedly generally correct, must be accepted as an "*a priori*" one. Extension of tumor growths in the cases in which it was noted was along the ureter or the periureteral tissues. In Glas' case, the extension involved the tissues surrounding the opposite ureter. Metastasis to the liver is mentioned seven times; metastasis to the lungs five times; metastasis to the lymph glands eight times. Involvement of the vertebra occurred once and of the spleen once.

Although we cannot as yet subscribe to the radical view that all papillomatous growths found in the ureter are malignant, we hold that they must be viewed with suspicion and subjected to a most thorough histologic study. We believe that the general histologic picture in the papillary types of tumors is relatively unimportant and that most careful and painstaking search should be made for atypical cells, atypical cell arrangement and cell invasion, with proper evaluation of these, before a satisfying conclusion can be reached as to the exact nature of such tumors. This will undoubtedly lead to the recognition of malignancy

23. Player, L. F.: Primary Ureteral Carcinoma, with Case Report and a Review of the Literature, *Urol. & Cutan. Rev.* **32**:438, 1929.

24. Janssen, P.: Aussergewöhnliche Tumorbefunde den oberen Abschnitten der Harnwege, *Ztschr. f. urol. Chir.* **9**:474, 1922.

25. Vorpahl, K. U. F.: Primary Carcinoma of the Ureter, *Am. J. Urol.* **2**:509, 1905.

26. Spiess, P.: Die primären epithelialen Tumoren des Nierenbeckens und des Ureters, *Centralbl. f. allg. Path. u. path. Anat.* **26**:553, 1915.

27. Walker, J. W. T.: *Proc. Roy. Soc. Med. (Sect. Urol.)* **14**:42, 1921.

per se in many growths that would otherwise be classified as benign and will lessen observation of metastasis from tumors apparently benign. That the so-called simple papillomas may at times evolve into tumors of entirely different character is certainly at least suggested by clinical and experimental data.

SUMMARY

A case of primary carcinoma of the ureter is reported, with a résumé of the salient features of the forty-eight cases recorded in medical literature. Twenty-eight of the recorded tumors were papillary; twenty were nonpapillary. The incidence is about equal for both sexes, with the greatest number occurring during the sixth and seventh decades of life. The lower part of the ureter is more frequently the site of the lesion. No etiology can be ascribed, although concurrent lithiasis was present in six cases. The consensus seems to be that so-called benign papillomas of the ureter and of other parts of the urinary tract must always be regarded as highly suspicious growths so far as actual, as well as potential, malignancy is concerned.

TESTICULAR TUBULAR ADENOMA OF THE OVARY

ITS ETIOLOGIC RELATION TO EMBRYONIC VESTIGES AND SPONTANEOUS SEX REVERSAL OF THE FEMALE GONADS

REPORT OF A CASE *

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The subject discussed here concerns one of the rarest tumors encountered in the ovary. Although this growth supposedly belongs to the group of nonteratoid tumors, its structure, its origin and its possible relation to hermaphroditism involve the general question of embryogenesis of the sex glands. It was Pick¹ who first described, in 1905, an unusual tubular adenoma of the ovary and designated it as adenoma tubulare ovarii testiculare. Since that time a few additional cases of similar tumors have been reported and live discussion of these tumors was brought up in recent years by Meyer,² Neumann³ and Heesch.⁴

Two points are essential in discussion of this pathology: 1. Do these tumors originate from the female or male germinal anlage, and if so, do they arise from differentiated sex cells or do they spring from undifferentiated sexual primordial elements that may or may not have any faculties toward sexual differentiation? 2. Should the presence of adenoma tubulare ovarii testiculare be considered as equivalent to hermaphroditism and interpreted as the result of prenatal misbuilding

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1. Pick, L.: Ueber Adenome der männlichen und weiblichen Keimdrüse bei Hermaphroditismus verus und spurius, Berl. klin. Wchnschr. **17**:502, 1905.

2. Meyer, R.: Drei Beiträge zur Kenntnis seltenerer Ovarialtumoren, Arch. f. Gynäk. **109**:212, 1918; Ueber einen Fall von doppelseitigen Ovotestis beim Neugeborenen sowie über besondere Formen der Keimdrüsen-Geschwülstbildung bei Pseudohermaphroditismus und Hermaphroditismus verus sowie über gleichartige Geschwülste bei nichtzwitterigen Personen, *ibid.* **123**:675, 1925.

3. Neumann, H. O.: Das tubuläre Adenom des Ovarium und seine Beziehungen zum Hermaphroditismus verus, Arch. f. Gynäk. **126**:553, 1925; Das Adenoma tubulare testiculare Ovotestis, Virchows Arch. f. path. Anat. **270**:501, 1928; Analoge Keimepithelblastome der Hoden und der Ovarien sowie ihr Vorkommen beim menschlichen Zwitter oder Scheinzwitter, Arch. f. Gynäk. **131**:477, 1927.

4. Heesch, O.: Zur Kritik der tubularen Ovarialadenome, Virchows Arch. f. path. Anat. **268**:280, 1928.

of the gonads, or should it be attributed to postnatal changes of the gonads and discussed in the light of present knowledge of sex reversal and intersexuality of the gonads?

These two questions are not easy to answer, especially in the case of the highest mammal (adult man). The questions of pathologic diagnosis and terminology present, also, great difficulties, if one may judge from the difference in opinion of the pathologists whom I have consulted on this case. One who favors and follows Pick's conception of the existence in the parenchyma of the ovary of tubular testicular anlage material has no difficulty in interpreting both the nature of this ovarian tumor and its relation to hermaphroditism. However, the presence of a differentiated tubular testicular anlage in the ovaries may be justly doubted, while the existence in the ovary of a true masculine homologue in the form of rete and tubuli recti may be accepted and these may be suggested as a possible source of this growth. Since there are two different opinions regarding the origin of the rete ovarii, the followers of the wolffian origin and the followers of the genital or germinal origin of the rete may tag these tumors accordingly. Ewing's⁵ forceful defense of the teratoid origin for embryonal alveolar and diffuse carcinomas of the testicle and L'Esperance's⁶ for embryonal carcinomas of the ovary may suggest the interpretation of the tumor under discussion as a one-sidedly developed teratoma. Still, if one is not inclined to go into details of the embryonic genesis of these tumors, he may simplify the whole matter by calling them simply hamartoma tubulare in the sense of Albrecht.

In pathologic discussion of these tumors the embryologic and experimental data concerning gonads must be considered, as it is undeniable that the rudimentary state of the sex glands and cellular deviations, or cellular misbuilding, without formation of organoid tumors is often met among cases of this type. A clinical course with considerable local destruction and but little tendency toward metastasis is rather characteristic of these tumors and this puts them into a specific group of ovarian neoplasms. The observed sexual deviations toward hermaphroditism, intersexuality and gynandromorphism, the changes in the menstrual cycle and the undeniable hormonal influence of these tumors on the remaining ovary and the body generally, necessitate special attention from the clinical point of view. The case in question bears also certain peculiar clinical and morphologic features that are of considerable interest.

5. Ewing, J.: Teratoma Testis and Its Derivatives, *Surg. Gynec. Obst.* **12**: 230, 1911.

6. L'Esperance, E. S.: Embryonal Carcinoma of the Ovary, *Arch. Path.* **5**:402, 1928.

REPORT OF CASE

A patient, aged 31, was admitted to the hospital on Sept. 27, 1925, with the following history:

She was married in February, 1922, and the first child was born in February, 1923. She nursed the infant for nine or ten months. Her menstrual function was fully reestablished in August, 1923, or about seven months after childbirth. She continued to menstruate regularly every twenty-eight days until February, 1924. She did not menstruate in March, but did not consider herself pregnant. The menstruation in April was perfectly normal without any unusual manifestation. She did not menstruate again until September, 1925; then she had a slight flow described as spotting. About six months previous to admission to the hospital, she was examined by Dr. W. B. Conner, who detected a movable tumor in the right quadrant of the pelvis. She was examined at intervals of one or two months without any apparent change being found in the size of the tumor.

On admission to the hospital, she appeared to be well developed and well nourished, generally robust and absolutely feminine. No anatomic abnormalities or defects were found. No evidence of sexual or psychic deviations was obtained from her past history or on physical examination. The family history in regard to congenital malformations, constitutional diseases or occurrence of twins was negative. Her first menstruation began at the age of 14, lasted on an average three days and remained always regular, moderate in amount and painless. No thyroid disorders were noted, and on admission the thyroid appeared normal. The breasts were quiescent with no signs of lacteal secretion. The heart and lungs were normal. The abdomen moved evenly with respiration. It was well covered with subcutaneous fat. No abnormalities in the distribution of the hair around the external genitalia and on the face were noted. The external genitalia appeared free from any pathologic changes of note. On palpation of the abdomen, no tenderness was elicited. Vaginal examination revealed the presence on the right side of a tumor that was freely movable and apparently not attached to the uterus. On account of its smoothness and density, a tentative diagnosis of solid tumor of the ovary was made. The laboratory observations, including the results of examination of the urine and blood and of the Wassermann test, were essentially negative.

On September 28, or six months after the detection of the tumor, the operation was performed, and a large solid tumor of the right ovary was removed. The tumor was encapsulated and there was no evidence of the tumor breaking through the capsule, nor was there any enlargement of the lymph nodes in the pelvic region. The other abdominal organs were normal. The left ovary was normal and appeared quiescent. The appendix was somewhat congested and for this reason was removed at operation. The abdomen was closed without drainage, and the operation was followed by a complete and uneventful recovery.

Gross Examination of Tumor.—On pathologic examination, the tissue received had the appearance of a pear-shaped, smooth, solid tumor measuring 8 by 6 cm. The attached ovary was flattened and compressed, and the hilar portion of it was fused with the tumor, which appeared to begin near the medullary portion of the hilar region of the ovary. The cut surface showed a solid, edematous, pinkish tumor, rather uniform in structure, well encapsulated and without evidence of degeneration, hemorrhages or cystic formations. While the central portions were harder and resembled somewhat soft fibroma or xanthoma, the subcapsular portions were more delicate and homogeneous. The cut surface of the ovarian portion was free from any evidence of recently formed or involuting corpora lutea, and

no fresh hemorrhages were noted. No follicular cysts were present, and the cortical portion of the ovary appeared uniformly fibrotic and free from any gross evidence of functional activity.

Microscopic Examination.—On microscopic examination, the sections had a varying appearance, depending on the portion of the tumor from which they were cut. The ovarian portion showed a smooth cortex, covered on the outer surface with high cuboidal, quiescent, germinal epithelium occasionally showing short abortive invaginations. Beneath it was seen a fibrous tunica albuginea that was poor in cells. The outer layer of the cortex contained only a few primordial follicles with occasional oocytes. In no place was a ripe follicle found. The primordial follicles revealed all the signs of degeneration, manifested by cicatrization and complete absence of follicular cystic degeneration. The theca interna was furnished with a single layer of low cuboidal epithelium, but neither the elements of the theca interna nor those of the theca externa showed transformation into lutein cells. A number of rather large corpora albicantia were seen, but no microscopic evidence of recent hemorrhages, hemochromatosis or unusual histiocytic activity was present. The medullary portion of the ovary consisted of loose connective tissue well supplied with blood vessels and lymphatics. Amid the stroma cells of the medullary portion were seen conspicuous small groups and islets of large, irregular, polygonal cells structurally corresponding to the paraganglionic cells or paraganglionic tissue described by Berger,⁷ Wallart,⁸ Winiwarter⁹ and others. In no way were these cellular inclusions related to the tumor growth. Neither tubular wolffian relics nor rete tubules were found. Just on the outer border of the hilum was seen a well defined margin of an epithelial tumor growth delimited on its outer surface not with the regular thick capsule but with only loose connective tissue furnished by the stroma of the hilum itself (fig. 1 *H.r.o.*). The architecture of the growth, on the whole, was that of an organoid tubular type and was represented by sheaths and groups of cells which formed solid strands, cylindric cords and tubules with an occasional axial lumen and surrounded by delicate partitions of connective tissue (fig. 1 *E.sh, Crd, Tbl, Prt*). Some of the tubules appeared well differentiated and some were lined with high cuboidal epithelium and supplied with true basement membrane (fig. 2 *B.m.*). The cells of the tumor were uniform in size with round or oval nuclei which contained one, and occasionally two, rather prominent nucleoli. The nuclear chromatin was arranged mostly in loose spirem, and only occasional mitoses were seen. The cytoplasm was indistinct; no clearly visible intercellular borders were seen, and the axial fusion of the cytoplasm gave in some places the appearance of syncytium-like structures. Nowhere were foci of necrosis, massive degeneration or perivascular arrangement found.

Among the cords and tubes, and intimately related to them, were seen strikingly different structures composed of large, clear, acidophilic cells. These clear cells were arranged mostly in groups, islets and voluminous masses, some of which even appeared like tubes, with axial lumen and basement membrane (fig. 3 *F.l.c.*). These cells varied in size, some reaching a diameter of 40 microns. They con-

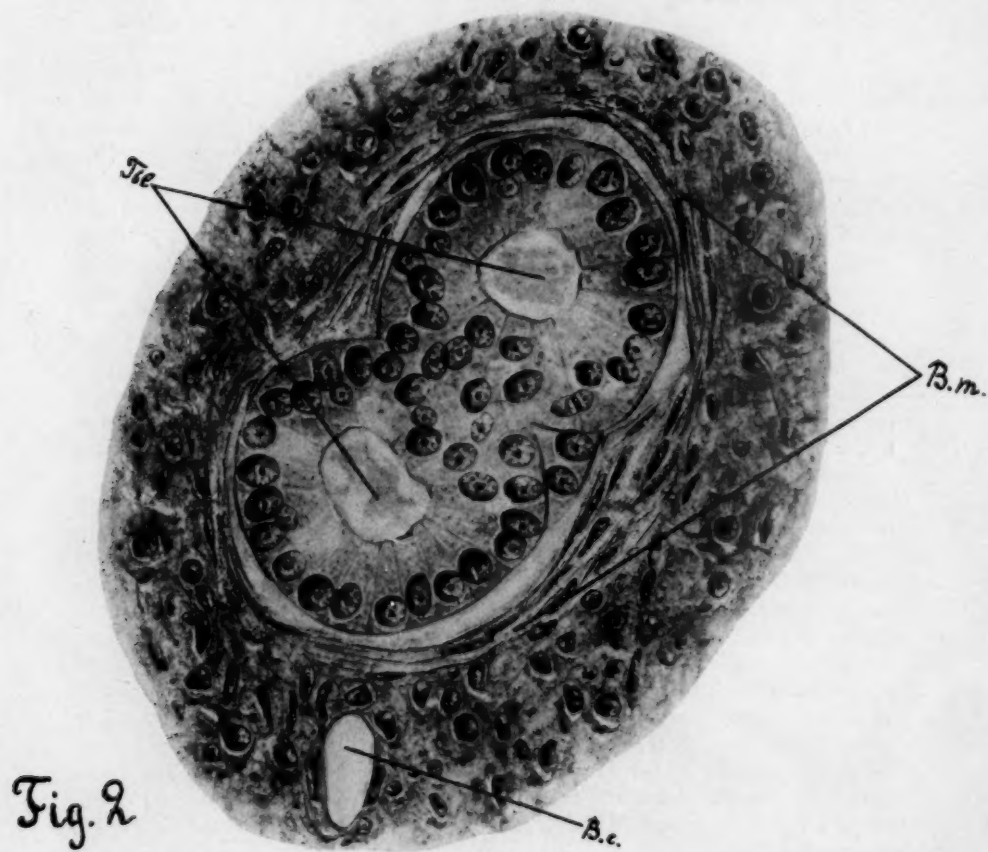
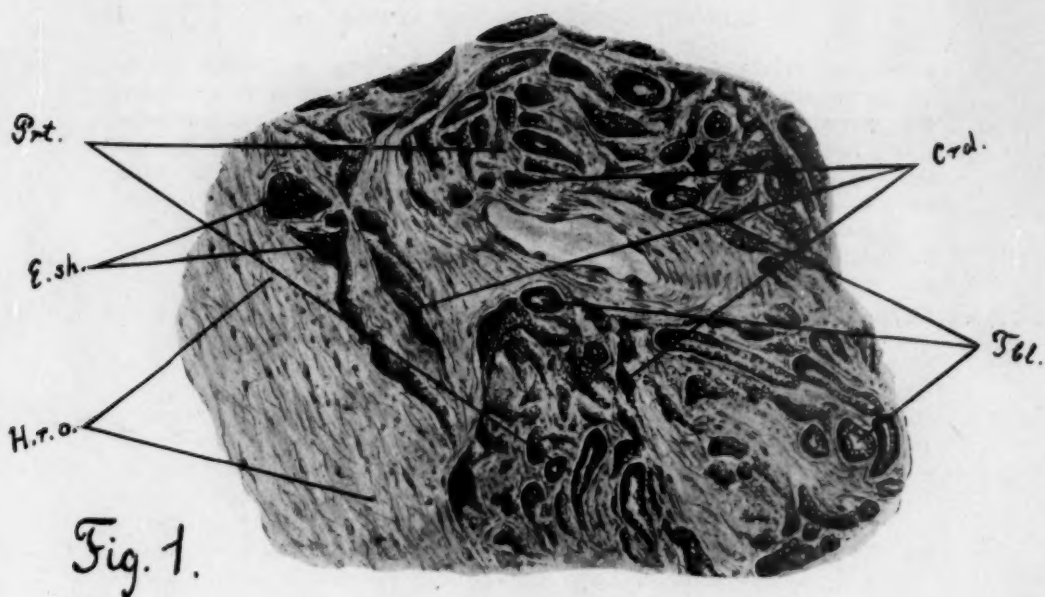
7. Berger, L.: La glande sympathicotrope du hile de l'ovaire humain, Arch. d'anat. d'histol. et d'embryol. **2**:259, 1923.

8. Wallart, J.: Sur le tissu paraganglionnaire de l'ovaire humain, Arch. d'anat. d'histol. et d'embryol. **7**:3, 1927.

9. Winiwarter, H.: A propos des cellules sympathicotropes de l'ovaire humain, Compt. rend. Soc. de biol. **89**:830, 1923; L'appareil phéochrome de l'ovaire humain, Bull. d'histol. appliq. à la physiol. **1**:145, 1924.

tained oval or round nuclei which appeared rather small in relation to the voluminous size of their cytoplasm. The most unusual feature of the nuclei was their polychromaticity. While some of the nuclei appeared vesicular and were clearly and lightly stained, the chromatin granules of others appeared coarse and the karyoplasm was stained deeply—almost black—so that no nuclear details could be recognized (fig. 3). The lightly stained nuclei showed a clearly visible nuclear membrane and usually one prominent nucleolus. These clear cells stood out conspicuously on account of their large size and the eosinophilic staining of their cytoplasm. In the cytoplasm of these large cells it was easy to see the dense perinuclear zone, not sharply delimited and deprived of vacuoles (fig. 3 *D.p.s.*), and the external zone having a clear aspect with vacuoles separated by thin cytoplasmic strands (fig. 3 *C.v.e.s.*). In the sections fixed in formaldehyde and stained with sudan III, these cellular inclusions were stained in orange red, proving thus their fatty nature. These clear acidophilic or fat-laden cells resembled more closely the interstitial cells, namely, those interstitial cells which originate in the embryonal ovary and testis among the medullary or sexual cords and which are formed from the epithelial elements of the cords undergoing a regressive process and fatty degeneration. In examining serial sections, it is hardly possible to confuse these clear cells with true lutein cells or the interstitial cells of Leydig. During the process of organoid transformation, the individual epithelial elements undergo rather characteristic changes manifested by gradual hypertrophy of the cytoplasm, increase in size and number of the granules and vacuoles (figs. 3 and 4), loss of intercellular boundaries and final transformation into huge, formless masses with nuclei stained black, gathered together and pushed to one side (fig. 5). This regressive metaplasia of the epithelial elements takes place slowly and is evidently determined to some extent by the process of vascularization. Wherever the capillaries penetrate into the structures and come into contact with the epithelial spherules, the latter begin to show gradual degeneration with accumulation of fat and final transformation into the structureless masses described (figs. 3 and 4 *B.c.*). There was no evidence of degeneration of the connective tissue stroma or of histiocytic and lymphoid infiltration. The appearance of the large, clear, fat-laden cells suggests the local fatty degeneration of the epithelial ingredients of the cords and not a fatty infiltration that determines the formation of mesenchymal ovarian lutein cells and the cells of Leydig.

The main bulk of the tumor was composed mostly of solid cords, tubes and irregularly arranged and closely packed epithelial cells forming a syncytium which may be regarded as the primordium of a Sertoli cell syncytium. The cords of the tumor were undoubtedly homologous to the medullary or sexual cords of the first proliferation and in the process of evolution showed transformation into tubules closely resembling young seminiferous tubules; but no nuclear changes indicative of further differentiation and the formation of spermatogonia were found in any section. The stroma of the tumor participated actively in the growth, and its distribution and relation to the epithelial anlage of the tumor suggest an unmistakable tendency toward dissociation of the cords, and this phenomenon may mean the initial step toward organogenesis. In the sections from the denser portion of the growth, the microscopic picture presented certain peculiarities deserving of special consideration. Here the epithelial cells appeared small and grouped together in masses, strands and sheaths without any definite organoid arrangement. The marginal portions of these sheaths showed gradual dedifferentiation and their cellular boundaries faded into surrounding cellular fibrous tissue. The latter appeared loose, edematous and free from lymphoid and histiocytic infiltration, and no such inclusions as muscle, cartilage or derivatives of the entoderm or ectoderm were found.



EXPLANATION OF FIGURES

All drawings were made with the aid of a camera lucida of Abbe: figure 1, with Bausch and Lomb 16 mm. objective, 10 ocular and tube half drawn; figures 2, 3, 4 and 5 with 4 mm. objective, 10 ocular and tube completely drawn.

Fig. 1.—Low magnification of a section of the tumor cut through the place of its attachment to the hilar region of the ovary (*H. r. o.*). The tumor growth is shown to consist of epithelial sheaths (*E. sh.*), cords (*Crd.*) and tubules (*Tbl.*) with delicate connective tissue partitions (*Prt.*).

Fig. 2.—Well formed tubes are seen, with axial lumen lined with a single layer of epithelium (*Tbl.*) and furnished with a basement membrane (*B. m.*).

Fig. 3.—Distinct organoid tubular structures appear here, the epithelial constituents of which undergo gradual hypertrophy and fatty degeneration with transformation into large, clear, fat-laden cells (*F. l. c.*) forming islets and huge rosets. Nuclear polychromaticity of the cells and deep staining of the karyoplasm are characteristic of these cells. The dense perinuclear zone (*D. p. z.*) and the clear vacuolar external zone (*C. v. e. z.*) are conspicuous. Blood capillaries (*B. c.*) with their relation to *F. l. c.* are shown.

Fig. 4.—A further step in the hypertrophy and degeneration of the epithelial formations, with an increase in the size of the granules, vacuoles and loss of intercellular boundaries.

Fig. 5.—The final stage in the degeneration, with transformation of the epithelial formations into huge, formless masses, the nuclei of which are stained black, gathered together and pushed to one side and the cytoplasm completely fused.

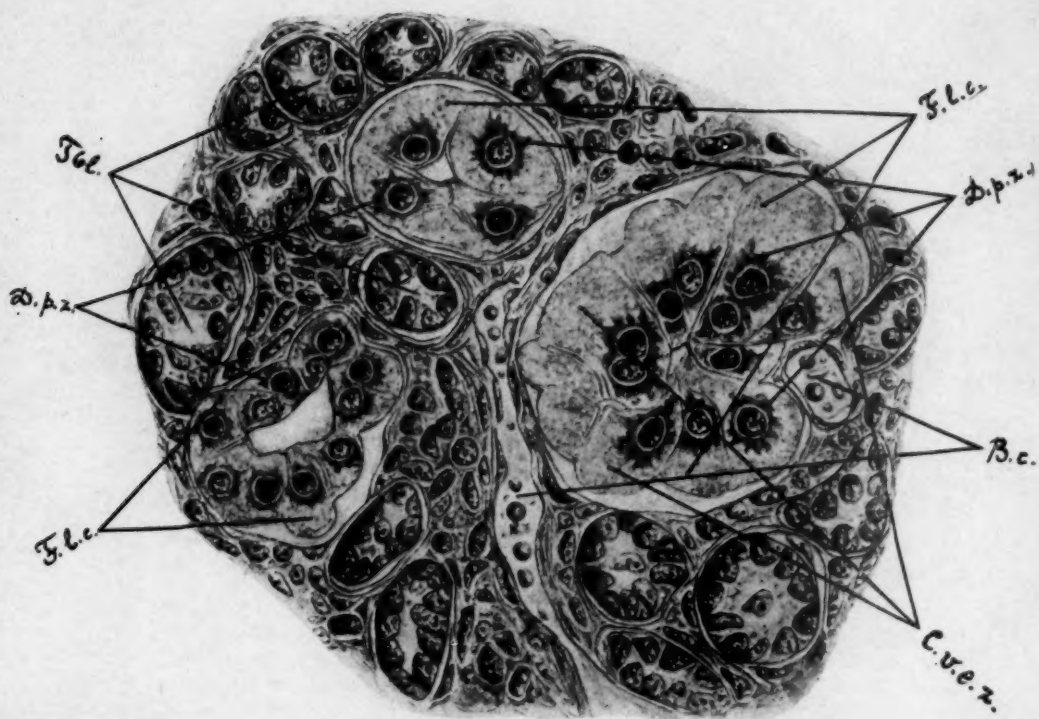


Fig. 3



Fig. 4.

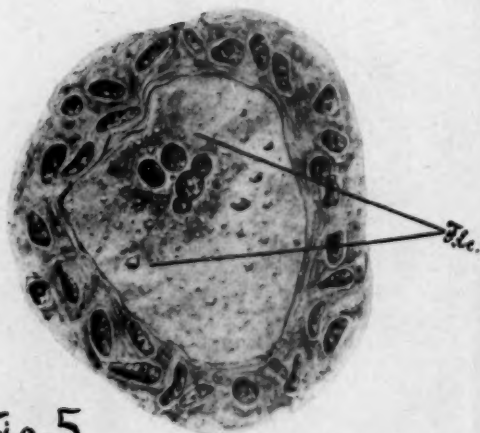


Fig. 5

COMMENT

The described picture is unusual enough to make the question of diagnosis a subject of considerable disagreement. By virtue of the embryologic complexity of the ovary certain tumors, and especially those arising in the hilum, will remain for a long time a matter of individual interpretation, which may be based either on pure embryologic data or on the general cellular appearance and clinical behavior. The nature of the tumor discussed cannot be understood without embryologic consideration, and its diagnosis can be settled only by the method of exclusion.

Here, in the region of the hilum and mesovarium, are found in the fetal life various complicated formations undergoing specific evolution and involution and thus affording every chance for different anomalies. Four of these embryologic formations which deserve chief consideration are: paroophoron, epoophoron, rete and the medullary cords of the first proliferation. Each of these ovarian inclusions has, in fetal life, its own developmental cycle, although they all remain unused in the final formation of the ovary. This fact offers an understandable source of various ovarian anomalies and pathologic conditions manifested by incomplete regressions of the aforementioned embryonic constituents of the fetal ovary, their misplacement and the pathologic formation of cysts, adenomas and carcinomas.

It is generally agreed now that paroophoron and epoophoron are of wolffian origin. The fates of these two wolffian derivatives are somewhat different. While the epoophoron shows until birth progressive evolution, the paroophoron undergoes regression soon, although it does not disappear entirely at the time of birth and during the first days of extrafetal life. The rapid involution of the latter accounts for the rarity of the paroophoric anomalies. Winiwarter¹⁰ observed besides paroophoric cyst formation an interesting anomaly, in a six months' ovary, of the nature of a true epithelial tumor somewhat resembling carcinoma. Anomalies of the epoophoron are more common, being manifested by simple enlargement of the tubules, their sacculation, the formation of simple and papillary cysts and diffuse proliferation of the epithelial lining with all the characteristics of malignant carcinomatous growth. These wolffian relics may present themselves either in the form of spheric, trabecular or compact epithelial collections resembling malpighian cells or in the form of tubes or cysts lined with cuboidal,

10. Winiwarter, H., and Sainmont, G.: Nouvelles recherches sur l'ovogenèse et l'organogenèse de l'ovaire des mammifères (chat), *Arch. de biol.* **24**:373, 1909; La constitution et l'involution du corps de Wolff et le développement du canal de Muller dans l'espèce humaine, *Arch. de biol.* **25**:169, 1910.

cylindric and often ciliated epithelium. According to Masson,¹¹ in addition to the various types of cysts, these embryonal vestiges may give origin to massive wolffian epitheliomas which may run the course of true carcinomas with lymph node involvement and generalization. In my case, in which no signs of cysts, or even microcysts, were found, the massive wolffian epithelioma only may be considered. Here I have to state what constitutes the wolffian epithelioma and what are the main histologic and clinical features of the so-called wolffian epithelioma.

From the descriptions of cases designated as cases of wolffian epithelioma (Delannoy and Breton,¹² Leveuf and Heraux,¹³ Corsy and Montpellier¹⁴) one gets the information that grossly, in the early stage, these tumors appear regular, round, sometimes pear-shaped, and encapsulated. The cut surface is grayish or reddish, with a marble-like appearance. Histologically, they are composed of epithelial cellular nests, strands, papillary arborescences and tubes lined with cuboidal or cylindric cells which are irregular in volume, contain basal nuclei and show intense chromatophilia, nuclear monstrosities and numerous mitoses. The stroma is rather vascular, myxomatous or dense and without collagen, and in its distribution and growth it does not show any tendency toward dissociation of the adjacent epithelium, a phenomenon that is observed in embryonal ovarian tumors arising from the germinal epithelium of the first proliferation (Peyron¹⁵). In some cases, the remnants of the ovary can be seen; in others, no remnants of the normal ovary are found. No preexisting Leydig's "Zwischenzellen" or interstitial cells of Turneux are found and no evidence of the transformation of the epithelial elements into clear or fat-laden cells is present and no Call-Exner bodies are formed. From the clinical point of view, no precocious virilism, sex changes, hirsutes or menstrual disturbances are associated with these wolffian tumors.

Comparing the structural features of my case with the description given of solid wolffian epitheliomas, one is left without justification for calling the tumor in question mesonephroma, a term too vague and

11. Masson, P.: Essai sur les tumeurs non-tératoides de l'ovaire, *Gynéc. et Obst.* **6**:81, 1922.

12. Delannoy, E., and Breton, A.: Un cas d'épithélioma Wolffien de l'ovaire, *Bull. Soc. d'obst. et de gynéc.* **4**:239, 1926.

13. Leveuf and Heraux: Un cas d'épithélioma Wolffien de l'ovaire chez une fillette de sept ans, *Ann. d'anat. path.* **3**:639, 1926.

14. Corsy, F., and Montpellier, J.: Sur les évolutions cellulaires le diagnostic histologique et les homologues des épithéliomes ovariens issus de vestiges Wolffiens, *Bull. de l'Assoc. franç. p. l'étude du cancer* **16**:537, 1927.

15. Peyron, A.: Sur les caractères et les tendances évolutive d'un type de tumeur ovarienne issu des cordons médullaires, *Compt. rend. Soc. de biol.* **90**:575, 1924.

groundless to apply. It is true that in spite of the epithelial lining resembling the wolffian lining certain types of tumors with rare regular lumina are difficult of diagnosis and can be attributed to medullary cords (Corsy-Montpellier¹⁴), but in my case there are other, more important features that speak against the diagnosis of mesonephroma. The transformation of epithelial formations into diffuse mesenchymal sheaths may resemble the structure of a mixed tumor of the kidney, but the other dominant characteristics of the growth in question could not be fitted to Wilm's congenital tumor, especially in a case like mine, in which the primary ovarian origin of the tumor is unquestioned.

The discussion of ovarian mesonephromas brings immediately the question of rete ovarii and its relation to ovarian neoplasms. Conflicting embryologic data in regard to the origin and fate of the rete ovarii leave the pathologist without true guidance in identifying, classifying and interpreting ovarian tumors arising from the rete. Under the term "rete," I understand the epithelial formations seated in the hilum of the ovary and extending into the mesovarium on one side and into the medullary substance on the other side. They present themselves in the form of solid epithelial buds and sometimes in the form of ramifying canals lined with cuboidal—or more seldom with cylindric—epithelium, are furnished with a delicate basement membrane and sometimes have smooth muscles around. For the reason that these epithelial formations are in relation by continuity or by contiguity on one side to the medullary cords and on the other side to the epoophoric tubes, two different opinions regarding their origin are offered.

According to Mihákovics,¹⁶ Sainmont,¹⁷ Winiwarter,¹⁸ Balfour¹⁹ and Wallart,²⁰ rete ovarii is homologous to rete testis and is of wolffian origin, while the seminiferous tubes are homologous to the medullary cords of the ovary and are derivatives of the germinal epithelium. According to Allen,²¹ Meyer,²² Felix,²³ Kingsbury²⁴ and Wilson,²⁵ the

16. Mihákovics, V.: Untersuchungen über die Entwicklung des Harn- und Geschlechtsapparates der Amnioten, Internat. Monatschr. f. Anat. u. Physiol. **2**:41, 1885.

17. Sainmont, G.: Recherches relative à l'organogenèse du testicule et de l'ovaire chez le chat, Arch. de biol. **22**:71, 1906.

18. Winiwarter (footnote 10, second reference).

19. Balfour, F. M.: On the Structure and Development of the Vertebrate Ovary, Quart. J. Mic. Sc. **18**:383, 1878.

20. Wallart, J.: Contribution à l'étude des origines du rete ovarii, Bull. d'histol. appliq. à la physiol. **5**:181, 1928.

21. Allen, B. M.: The Embryonic Development of the Ovary and Testis of the Mammals, Am. J. Anat. **3**:89, 1904.

22. Meyer, R.: Zur Kenntnis der kranialen und kaudalen Reste des Wolff'schen (Gartner'schen) Gänge beim Weibe, Centralbl. f. Gynäk. **7**:203, 1907.

rete ovarii is of germinal celomic origin and the observed communication between the rete and epoophoric tubes is considered by advocates of the germinal theory as accidental. Wallart's²⁰ case of ovarian aplasia, in which gradual and uninterrupted evolution of the epoophoric tubes into branchings characteristic of rete could be positively traced, seems to corroborate the fundamental studies of Sainmont and Winiwarter and at least brings new evidence for the wolffian origin of the rete.

The rete ovarii is well developed in the fetus and in the new-born infant, but in adults it is almost always found in more or less rudimentary form. In certain periods of life, for example in gestation, its lining epithelium becomes high cylindric and sometimes is furnished with a border of vibrating cilia. According to Winiwarter,¹⁰ the anomalies derived from the rete are as a rule more common than those from the epoophoron, and they appear in the second half of gestation and tend to affect the mesovarian and intra-ovarian portions more often than the epoophoric portion. Cystic papillomatous cavitations, cystic tubes and voluminous postnatal cysts are the main pathologic abnormalities of rete origin. Winiwarter believed that rete cysts, developing toward the end of gestation, are influenced by interstitial tissue. His observations on the interrelation between developmental growth of the rete and the apparition of interstitial cells on one side and the developmental arrest of the rete shortly after birth with degeneration of the mesovarian interstitial cells on the other side, is of great significance. He attributed this phenomenon to the trophic influence of the interstitial tissue, but in the light of the latest work on ovarian grafts, x-ray action on the young ovary and free-martin intersexuality, his observations may be interpreted by the advocates of the germinal origin of the rete differently and with conclusions casting doubt on the extragenital origin of the rete. This brings us to the discussion of the fourth, last and most important constituent of the fetal ovary, namely, medullary cords, the anomalies of which have immediate bearing on the origin of the tumor in question.

The germinal origin of the medullary cords is definitely established and generally accepted. During the development of the gonads, the germinal epithelium gives, according to Winiwarter and Sainmont, three successive proliferations, each characterized by its particular evolution. At the early stage, the stage of indifferent sexuality, the first prolifera-

23. Felix, W.: The Development of the Urinogenital Organs, Manual of Human Embryology, F. Keibel and F. Mall, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 752.

24. Kingsbury, B. F.: The Morphogenesis of the Mammalian Ovary: *Felis Domestica*, Am. J. Anat. **15**:345, 1913.

25. Wilson, K. M.: Origin and Development of the Rete Ovarii and the Rete Testis in the Human Embryo, *Contrib. Embryol.* **17**:69, 1926.

tion of the germinal epithelium gives rise, by invagination, to thick, plain, cellular cords, ramifying and anastomosing and encroaching on subjacent connective tissue. After they break their relation with the germinal epithelium, the cords are destined to become seminiferous tubes and in the ovary they remain as abortive seminiferous tubes, known as medullary cords. Thus, under the term medullary cords are understood the epithelial formations of the fetal ovary deriving from the first proliferation of the germinal epithelium and homologous to the seminiferous tubes in the male. If the gonad is destined to become a male gonad, the cords perfect themselves, lose their lateral anastomoses and organize into true seminiferous tubes. The germinal epithelium covering the surface of the gland disappears, the connective tissue undergoes condensation and forms testicular albuginea and between the tubules there appear large acidophilic interstitial cells. In the gonad that is destined to become an ovary, the germinal epithelium, after having produced the medullary cords, does not lose its aptitude to multiply and forms the second set of sexual cords—the cords of Valentin-Pflüger—which arise as a secondary proliferation of the germinal epithelium. According to Winiwarter and Sainmont, Valentin-Pflüger's cords of the ovary transform themselves into primordial follicles without giving rise to primitive ovules. Some of them reach only the stage of primordial follicles; others are transformed into graafian follicles, more or less voluminous but with the same doom awaiting them. After degeneration of the derivatives of the second proliferation—degeneration which occurs after birth—the germinal epithelium undergoes a new period of multiplication by invagination and it is from the cellular colonies of this third proliferation that a definite cortical zone and definite ovary are formed. While the genital portion of the mesonephron in the male gonad takes an actual part in the building of the genital organs and forms the proximal part of the efferent ducts, in the female it remains nonfunctioning and absolutely rudimentary as the rete ovarii and efferent canaliculi of the epoophoron. The tubular embryonic duality persists rudimentarily but constantly and as an unutilized tubular constituent remains in the ovary in the form of embryonic vestiges giving rise to the anomalies described.

If the degeneration of the medullary cords led to their complete and indisputable disappearance, the anomalies arising from the medullary cords should not take place at all. However, it is admitted now that certain genital anomalies, for instance spontaneous sex reversal or the experimental transformation of the ovary into testis or ovotestis, have to be interpreted either as the result of the presence within the ovary of the remains of medullary cords or as a manifestation of the retained potency of the germinal peritoneal epithelium to proliferate

and, by duplicating the embryonic process, to form anew the sex cords in such ovaries. This possible dual source of morphologic disturbances of the ovaries must be considered always in the studies of certain embryonic ovarian tumors. The development of such tumors is in many instances preceded by profound changes of the gonads with hyperplasia of the embryonic epithelial vestiges and their gradual organoid arrangement and transformation into intersexual glands or ovotestes. During these changes the female structures of the ovarian cortex undergo regression, and with their disappearance the ovary loses control over the embryonic vestiges, which then begin to grow, differentiate in the male direction and later by their hormonal action influence the secondary sex character. Thus clinical manifestations with disturbance or suppression of menstruation and the psychic and somatic stigmas of masculinization find explanation and should be expected in cases of embryonal tumors of germinal origin. This suggests that such tumors are etiologically related to gonadic misbuilding and disturbances and often are the sequence of the latter.

The earlier investigators of tubular adenomas of the ovary (Pick,¹ Schickele²⁶) were inclined to associate these tumors always with hermaphroditism or pseudohermaphroditism. Neumann³ and Meyer² insisted justly that, although such tumors are more common in persons with rudimentary genitalia, they may occur as well in perfectly normal women. Of course Pick's definition of hermaphroditism differs from that generally employed. According to Pick, essential hermaphroditism lies in the mixing of germinal sexual characters or the union of male and female characters independently of order, degree of development or actual stage of morphologic sexual differentiation. The zoologic definition of hermaphroditism implies the union in the same person of the primary sexual characters of both sexes or the simultaneous existence of female and male gonads (Caridroit²⁷). Meyer's opinion, as I shall show later, has more reason to be accepted than that of Pick since it is backed by the substantial support of zoologists with their more exact methods of observation and experimentation.

Neumann, trying to reconcile the opposite opinions of Meyer and Pick, asked why one should not use instead of the term hermaphroditism the term "potential hermaphroditism." This term, of course, may be proper in a physiologic sense, but morphologically it sounds one-sided and meaningless as compared with the zoologic term sex reversal or

26. Schickele, G.: Adenoma Tubulare Ovarii (Testiculare), Beitr. z. Geburtsh. u. Gynäk. **11**:263, 1907.

27. Caridroit, F.: Étude histo-physiologique de la transplantation testiculaire et ovarienne chez le gallinacés, Bull. biol. de la France et de la Belgique **59-60**:135, 1925-1926.

intersexuality. The latter term designates the state of the gonad which changes its sex spontaneously or experimentally, prenatally or postnatally, and undergoes structural evolution with transformation of the ovary into ovotestis or rudimentary testis. Strictly speaking, there is no true hermaphroditism in man, since true hermaphroditism means the union of the organs of two sexes which are capable of functioning, and the last or simultaneous and successive formation of two sorts of gametes in the same organ has never been observed (Lacassagne²⁸). The term hermaphroditism, said Professor Lillie,²⁹ has so many connotations that it seems better to drop it from one's vocabulary so far as mammals are concerned and designate these questionable sexual anomalies under the head of intersexual. His own work and the work of his associates on free-martins should be consulted by medical students of this problem, since it gives essential information, closely related to the pathology of the human ovary and its embryonal neoplasms of the tubular testicular type.

In order to understand the part which medullary cords may play, both in sexual metamorphosis of the female gonad and in etiology of the tubular testicular adenomas, one must first briefly review the latest work on gonadic transformation in free-martins, after x-ray irradiation, in ovarian grafts and after a left-side oophorectomy in birds. This review will contribute, in addition, a great deal to a proper interpretation of the nature of the large, clear, fat-laden cells present also in the tumor described by me and wrongly interpreted by some writers on ovarian testicular adenomas as interstitial Zwischenzellen.

Under the term free-martin, I understand a female which is born a co-twin with a normal male of cattle, goats or pigs and which has the internal reproductive organs of the male type and the external genitalia of the female type. At first it was considered as an abnormal male, but later the conclusion was reached that primarily the free-martin gonad is female in structure and that secondarily it is transformed into a male gonad. In accordance with the degree of transformation, the gonads of the free-martin are divided into three groups characterized respectively as the low, the medium and the high degree of transformation in the male direction (Willier³⁰). Gonads of the "low degree" of transformation are characterized by an undescended or ovarian position, by the absence of epididymis, by the

28. Lacassagne, A.: La question de l'hermaphroditisme chez l'homme et les mammifères, *Gynéc. et obst.* **1**:273, 1920.

29. Lillie, F. R.: The Free-Martin: A Study of the Action of Sex Hormones in the Foetal Life of Cattle, *J. Exper. Zool.* **23**:371, 1917.

30. Willier, B. H.: Structures and Homologies of Free-Martin Gonads, *J. Exper. Zool.* **33**:63, 1921.

small size and low degree of the organization of the sex cords and by a large and well differentiated rete, penetrating to the posterior end of the medullary cords but still retaining its primitive position at the hilum of the ovary. Gonads of the "medium degree" of transformation show a further step toward testicular organization. The gonads still retain the ovarian position, but the sex cords appear larger and show a high degree of organization with the establishment of a connection with the rete cords. Two types of sexual cords are recognizable: One type resembles the medullary cords and the other seminiferous tubules. The former corresponds in its appearance to the medullary cords of the normal ovary, being composed of solid strands and cords or irregularly arranged and closely packed epithelial cells forming a syncytium which may be regarded as the primordium of a Sertoli cell syncytium. The transition between medullary cords and seminiferous tubules can be definitely observed at this stage. The gonads of the "high degree" of transformation are descended to a position in the groin, the seminiferous tubules are well differentiated, the tubuli recti connect the rete tubules with the seminiferous tubules, the rete tubules connect with the vasa efferentia, the epididymis is typically male and a typical spermatic cord is present.

The described phenomenon of the gradual transformation of the gonad demonstrates that a gonad with a primary female determination may form a structure which is morphologically a testis. This is accomplished through suppression of the cortex and overdevelopment of the medullary cords and urogenital union. The observation on free-martins proves that the gonad of mammalian female zygotes is capable of a series of transformations that may exist between an ovary and a testis. I shall discuss later the nature of the etiologic factors causing such transformation. Having presented the conceptions of Lillie,²⁹ Willier,³⁰ Hughes³¹ and Chapin,³² I shall proceed with a discussion of post-irradiation transformation of the ovaries.

In a series of publications, Brambell, Parkes and Fielding³³ presented important observations on the morphologic changes that take place in the ovary of the mouse following exposure to x-rays before

31. Hughes, W.: The Free-Martin Condition in Swine, *Anat. Rec.* **41**:213, 1929.

32. Chapin, C. L.: A Microscopic Study of the Reproductive System of Foetal Free-Martins, *J. Exper. Zool.* **23**:453, 1917.

33. Brambell, F.; Parkes, A., and Fielding, U.: Changes in the Ovary of the Mouse Following Exposure to X-Ray: Irradiation at Three Weeks Old, *Proc. Roy. Soc. London (ser. B.)* **101**:29, 1927; Changes in the Ovary of the Mouse Following Exposure to X-Ray: Irradiation at or Before Birth, *ibid.* **101**:95, 1927. Brambell, F., and Parkes, A.: Changes in the Ovary of the Mouse Following Exposure to X-Ray: Irradiation of the Nonparous Adult, *ibid.* **101**:316, 1927.

birth, at birth and at the age of 3 weeks. In the case of irradiation of the ovary of the mouse at 3 weeks of age, following destruction of the follicles, the ovary shows, at about the twenty-fourth postirradiation day, a remarkable phenomenon manifested by proliferation of the germinal epithelium and its growth into the cortex in the form of thick, finger-shaped cords carrying with them a layer of cells of the tunica albuginea. When the cords reach the hilar region of the medulla, their growth ceases, the germinal epithelium stops proliferating and becomes thin and inactive and the cells composing the cords undergo hypertrophy, accumulate fat globules and transform into large, clear cells strikingly resembling luteal tissue. The fact that at this stage these fat-laden, clear cells are still in the form of finger-shaped cords with only thin connective tissue sheaths serves to distinguish them from corpora lutea vera or from corpora lutea atretica. The ovaries of some animals appear to remain in this stage and never go beyond it, however long they are observed. The ovaries of other animals, having arrived at this stage, undergo still further changes. The germinal epithelium reveals a second proliferation, distinct from the first, with the production of small masses or cords of cells which become separated from the surface epithelium almost as soon as they are formed. The tunica albuginea contributes connective tissue sheaths to these cords of the second proliferation and the nuclei of some of the cord cells become slightly enlarged, exhibit mitoses and undergo evolutionary changes suggestive of spermatogonia in embryonic testicular tubules. As Brambell stated, the epithelial cords of the second postirradiation proliferation of the germinal epithelium tempt comparison with those which during embryonic and prepubertal life normally take part in the organogenesis of the mammalian gonads. The origin of the cords of both the first and the second postirradiation is similar to that of the medullary and cortical cords of the normal ovary and of the spermatogenic tubules of the testis. The resemblance of these cords of the second proliferation to the structures described as spermatogenic tubules is remarkable. Thus, after exposure to the x-rays, the female gonad of the young mouse shows all the morphologic signs of sex reversal, with the formation of cords which are similar in every way to the sex cords of the free-martin.

When ovarian grafts are made in embryonic chicks (Greenwood³⁴), and in young chicks (Greenwood,³⁵ Finlay³⁶) and when ovarian auto-

34. Greenwood, A. W.: Gonad Grafts in Embryonic Chicks and Their Relation to Sexual Differentiation, *Brit. J. Exper. Biol.* **2**:165, 1924-1925.

35. Greenwood, A. W.: Gonad Grafts in the Fowls, *Brit. J. Exper. Biol.* **2**: 469, 1924-1925.

36. Finlay, G. F.: Studies on Sex Differentiation in Fowls, *Brit. J. Exper. Biol.* **2**:439, 1924-1925.

plastic transplants are made to hens (Caridroit,²⁷ Benoit³⁷), the grafts may show remarkable changes in the direction of sex reversal. Here these changes may show all grades of morphologic evolution beginning first with the formation of irregular epithelial structures resembling syncytium, then development of the cords and finally differentiation into tubes resembling absolutely the seminiferous tubes of normal testicles. The epithelial elements which have not shown evolutionary differentiation become loaded with fat and are destined to give rise to clear cells like interstitial cells, which differ from the mesenchymal Leydig's cells and for this reason are called by Caridroit simply "cellules claires." The source of the described syncytial formations, cords and tubes in ovarian grafts, according to Caridroit,²⁷ may be triple: (1) the germinal epithelium; (2) nonutilized medullary cords of the first proliferation lodged in the theca and not transformed into clear cells, and (3) stroma cords arising from the secondary embryonic proliferation. The rapid neoformation of a testicular nature that takes place in the autoplasmic ovarian transplants repeats completely the embryonal process, and the graft undergoing such transformation into a testis should be called an intersexual gland.

In both spontaneous sex reversal in the hen (Fell³⁸) and in testicular transformation of the right gonad after left side oophorectomy in the hen (Benoit³⁹) the process of transformation follows the same sequence of changes as were described for ovarian grafts. It is important to mention here that the fragments of the left ovary which have escaped during oophorectomy may regenerate and transform themselves into an organ composed of cords and tubes of male aspect (Benoit³⁷).

All investigators on sex reversal come to the following conclusions: (1) that the testes are remarkably stable while the ovaries possess a certain instability; (2) that the right ovary exhibits testicular transformation more often than the left one and (3) that in sex reversal or hermaphroditism in which an ovotestis is present the spermatic tissue occurs most commonly median to the ovarian position. The embryologic development of the gonads furnishes an explanation for the first conclusion regarding the stability of the testis. As Lillie²⁹ stated: "Theoretically we would have to assume that the male zygote contains female as well as male factors, but the male zygote may not be capable of such extensive transformation as the female, owing to the embryologic fact

37. Benoit, J.: Origine des cordons sexuels d'aspect male apparus dans des régénérat et des greffons ovariens chez la poule, *Compt. rend. Soc. de biol.* **94**:875, 1926.

38. Fell, H. B.: Histological Studies of the Gonads of the Fowl, *Brit. J. Exper. Biol.* **1**:97, 1923-1924.

39. Benoit, J.: États sexuels différents successifs obtenus expérimentalement chez une même poule, *Compt. rend. Soc. de biol.* **94**:1380, 1926.

that the male gonad never forms normally any homologue of the cords of Pfluger in the female, i. e., of the ovarian cortex, whereas the female does form the homologue of seminiferous tubules before the cords of Pfluger begin to arise." An additional reason for the stability of the male gonad is that since the early sex differentiation of the female presumably takes place solely under zygotic control while differentiation of the male is controlled by sex hormones, the introduction of female substance into the male system is without effect on the growth of the testes. The primary action of the sex hormones is the inhibition of growth of germinal epithelium. Thus, the introduction of male substance into the female system may overcome zygotic influence and suppress the growth of the cortex (Hughes⁴¹).

The preponderance of gonadic disturbances on the right side in the female is not limited to the lower vertebrates or birds only. If one reexamines the reports of cases of sex reversal or hermaphroditism in higher animals and in the human species, one finds also the predominance of right-side disturbances. This is not a simple coincidence, but evidently is the result either of quantitative inequality of the gonads or certain mechanical and vascular factors that make the ovary of the left side more stable as compared with the right one. Of nine pigs of intergrade sex, described by Baker,⁴⁰ seven showed testes on both sides and two, testes only on the right side, a normal ovary being present on the left side. In Corner's⁴¹ hermaphroditic adult pig, a testis with epididymis was found on the right side in place of an ovary. Nine reports of cases of hermaphroditism collected by Pick⁴² show the same predominance of a right-side disturbance. Three of these reports do not have any data concerning a left-side gonad, and yet in spite of this and the absence of germ cells in the testicular portion Pick classifies the cases as cases of hermaphroditismus verus. A striking predominance of male or mixed gonads on the right side in human hermaphroditism is evident from publications by various authors. Of eight reports of cases of human hermaphroditism collected by Lacassagne,⁴³ four dealt with mixed glands or ovotestes found only on the right side; two with ovotestes found on both sides; one with a testis found on the left side and an ovotestis on the right side and one with a true testis found on the right side and an ovary found on the left side. Baldwin's⁴⁴ patient

40. Baker, J. R.: On Sex Intergrade Pigs: Their Anatomy, Genetics and Developmental Physiology, *Brit. J. Exper. Biol.* **2**:247, 1924-1925.

41. Corner, G. W.: A Case of True Lateral Hermaphroditism in a Pig with Functional Ovary, *Contrib. Embryol.* **54**:137, 1920.

42. Pick, L.: Ueber den wahren Hermaphroditismus des Menschen und der Säugetiere, *Arch. f. mikr. Anat.* **84**:119, 1914.

43. Baldwin, J. F.: Lateral Partial Glandular Hermaphroditismus, *Am. J. Obst. & Gynec.* **2**:640, 1921.

had, on the right side, testicular tissue and on the left side, an ovary. Of eight reports of cases of gonadic tumor with probably a male gonad on the other side, collected by Neumann,⁴⁴ all describe right gonads showing male elements. According to Simpson (quoted by Willier⁸⁰), in the human female the left-side gonad is of pure female type, and disturbances, if present, are usually found in that on the right side. Zoologic observations show that disturbances in relation of parts in the fetal stage are found most commonly on the right side and that differentiation of ovarian tissue does not proceed so far in the right ovary as in the left. Thus the right ovary, as less differentiated tissue, is more capable of completing its differentiation or redifferentiation in a testicular direction than is the more highly differentiated tissue of the left ovary. About 65 per cent of young calves show the left ovary to be larger than the right, and the follicles more advanced. In birds, the right ovary is a rudimentary ovary (Riddle⁴⁵) or, according to Benoit,⁸⁰ it is a rudimentary testicle, and after a left oophorectomy this rudimentary right gonad shows definite redifferentiation in a testicular direction. Firket's⁴⁶ and Swift's⁴⁷ studies on the primordial germ cells of the chick explain this phenomenon on the basis of an initial primitive quantitative inequality of the two gonads as the result of an uneven distribution of the germ cells such that a greater number of germ cells lodged in the left genital ridge than in the right. These interesting embryologic observations may serve as a supplement to both the theory of a better supply of blood to the left ovary and the theory of a sex hormone.

The experimental material and observations that have been presented contribute greatly to the proper understanding of prenatal and postnatal gonadic misbuilding and, in addition, this knowledge of the sex reversal of the ovaries removes the necessity of associating testicular adenomas of the ovary always with hermaphroditism. Histologic study of the ovotestis indicates that the mixed gland originally was a normal ovary which progressively changed into a testis. Male transformation of the ovary has its cause in the glandular tissue itself. This means that in case of gonadic transformation no new structures are formed, and the testicular tissue found does not constitute a sort of extrinsic tumor, for a primordium of each male structure developed is present in the ovary at the time of sex differentiation. Gonadic redifferentiation of the

44. Neumann (footnote 3, third reference).

45. Riddle, O.: On the Sexuality of the Right Ovary of Birds, *Anat. Rec.* **30**:365, 1925.

46. Firket, J.: Recherches sur l'organogenèse des glandes sexuelles chez les oiseaux, *Arch. de biol.* **29**:201, 1914.

47. Swift, C. H.: Origin of the Definitive Sex Cells in the Female Chick, *Am. J. Anat.* **18**:441, 1915.

ovary in the male direction is observed in various conditions, and sex reversal can be influenced or initiated by various factors. For instance, spayed females of certain birds and animals tend to develop male characters; heifers with cystic degeneration of the ovary reveal the same tendencies; excessive egg-laying in birds may stimulate a new proliferation of sex cords; abdominal pathology, abdominal tuberculosis, surgical trauma, hemorrhages and ovarian neoplasms can also initiate redifferentiation of the ovary in the male direction. It appears that diminution of the ovarian mass or anything causing suppression of the ovarian cortex or leading to the degeneration of the follicles and diminution of the number of oocytes can upset the balance held by the oocytes, and possibly by the membrana granulosa, as female tissues acting against masculinizing substances, and initiate either organoid or neoplastic growth of male epithelial formations arising from the cords of the first and the second proliferation (Crew,⁴⁸ Caridroit,²⁷ Masson,¹¹ Masson, Chalier and Martin⁴⁹). It is interesting to mention here that neoplasms of the seminiferous type arising from medullary cords of the first proliferation are not found in mares, and this may be explained on the embryologic basis that no first proliferation initially male is observed in the development of the mare's ovary (Corsy⁵⁰). The quoted work of Brambell, Parkes and Fielding shows that the initial stage of sex reversal can be produced experimentally in the mouse by the action of the x-rays on the ovary and that in this case the germinal epithelium itself can give rise to a new proliferation in the form of sex cords. Keller's⁵¹ studies on normal and pathologic activity of the germinal epithelium in various types of adult ovaries collected by Champy favor such a possibility, especially in pathologic conditions. Keller mentioned also that small invaginations of the germinal epithelium may form nodules resembling in every way interstitial tissue. In cases of sex reversal in pigeons, the sex cords, according to Brambell,⁵² are derived from large clear islet cells genetically related to medullary cords and scattered in the ovarian stroma and in the theca, and morphologically resembling in every respect the luteal or interstitial cells of other authors.

48. Crew, F. A.: Studies in Intersexuality, Proc. Roy. Soc. London (ser. B) **95**:90, 1923; **95**:226, 1924.

49. Masson, P.; Chalier, A., and Martin, J.: Varicocèle tubo-ovarien. Oo-testis avec adénomatose testiculaire diffuse, Ann. d'anat. path. **2**:445, 1925.

50. Corsy, F.: Les néoplasies du testicule du cheval et leur importance pour l'embryologie et la pathologie générales de l'épithélioma sémmière, Bull. de l'Assoc. franç. p. l'étude du cancer **16**:218, 1927.

51. Keller, T.: L'activité normale et pathologique de l'épithélium germinatif de l'ovaire adulte, Gynéc. et obst. **17**:10, 1928.

52. Brambell, F.: Sex Reversal in a Pigeon, Proc. Roy. Soc. London (ser. B) **104**:459, 1929.

In my case, the growth reached a considerable degree of differentiation with morphologic formations of embryonic male type. The hormonal influence was sufficient to cause the general changes with suppression of the cortical activity of both ovaries and consequent cessation of menstruation. No signs of secondary sex changes were present, and nothing would justify the association of the tumor in my case with hermaphroditism in the biologic sense. This proves once more the correctness of Meyer's⁵³ opinion regarding the occurrence of testicular tubular adenomas in nonhermaphroditic persons. Shortly after removal of the tumor, normal menstruation was reestablished, and in May, 1928, the patient was readmitted to this hospital and gave birth to a perfectly normal female child.

The discussion presented amplifies to a great extent the difficult question of the origin of tubular testicular adenomas of the ovary, and also increases one's knowledge of various possibilities and causes of ovarian sex reversal. The presence of cells like lutein or interstitial cells in this tumor necessitates more careful morphologic differentiation between true *Zwischencellen*, or Leydig's interstitial cells of connective tissue origin, and the large, clear, fat-laden cells present in my tumor and found also in embryonic ovaries and testicles, and originating from epithelial elements of medullary or sex cords (Brambell,⁵⁴ Nonidez,⁵⁵ Simkins,⁵⁶ Popoff,⁵⁷ Caridroit,²⁷ Benoit,⁵⁸ Athias⁵⁹ and Aron⁶⁰). The fact that in most of these tumors the spermatic tissue occurs median to the ovarian position may be explained by the favorable conditions existing in the hilum, where loose connective tissue and good vascularization offer better facilities for the growth of sex cords than do the dense structures of the cortex (Fell³⁸).

53. Prof. Dr. Robert Meyer, of Berlin, examined the slides submitted and gave his help in the matter of diagnosis.

54. Brambell (footnotes 33 and 52).

55. Nonidez, J. F.: Studies on the Gonads of the Fowl: The Intertubular Tissue of the Testis in Normal and Henfeathered Cocks, *Am. J. Anat.* **34**:359, 1924; Studies on the Gonads of the Fowl: The Effect of Ligation of the Vas Deferens on the Structure of Testis, *ibid.* **34**:393, 1924.

56. Simkins, C. S.: Origin of the Sex Cells in Man, *Am. J. Anat.* **41**:249, 1928.

57. Popoff, N.: Le tissu interstitiel et les corps jaunes de l'ovaire, *Arch. de biol.* **26**:483, 1911.

58. Benoit, J.: Sur l'origine des cellules interstitielles de l'ovaire de la poule, *Compt. rend. Soc. de biol.* **94**:873, 1926.

59. Athias, M.: Recherches sur les cellules intestitielles de l'ovaire des cheirop-
tères, *Arch. de biol.* **30**:89, 1920.

60. Aron, M.: Sur la glande interstitielle du testicule embryonnaire chez les mammifères, *Compt. rend. Soc. de biol.* **85**:107, 1921.

CONCLUSIONS

A case is described of tubular testicular adenoma of the ovary which occurred in a woman free from any signs of hermaphroditism.

Biologic observations and experimental data on sex reversal and gonadic disturbances of the ovary are presented and commented on, and the conclusion is drawn that morphologic peculiarities of the ovary and biologic factors determining sex differentiation offer a logical explanation of spontaneous reactivation of the medullary cords, and even of the germinal epithelium, with the consequent organoid transformation in a male and neoplastic direction.

In studies of clinical material and in histologic research in the ovary, attention should always be given to a full recording of the observations in both gonads and to a quantitative study of the occurrence of gonadic disturbances on the right side.

The large, clear, fat-laden cells found in tubular testicular adenomas and originating from epithelial elements of medullary or sex cords should not be confused with true interstitial cells of connective tissue origin.

Embryologic considerations, zoologic observations and experimental data give every preference to the term sex reversal or intersexuality rather than the meaningless term hermaphroditism which is generally used now.

DETORSION DEFECTS IN CONGENITAL CARDIAC ANOMALIES

REPORT OF THREE CASES, WITH AN ANALYSIS OF THE MECHANISM OF THEIR FORMATION *

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Although congenital deformities of the heart are rather infrequent, in the course of time there has appeared in the literature an impressive number of reports of cases. The anomalies appear in infinite variety. They form endless combinations of various cardiac abnormalities with one another and with associated defects in other organs. Despite the complexities which they sometimes offer, they subscribe to definite anatomic laws, and by them may be analyzed. This and the fact that each case lends an insight into normal cardiac embryology and into its vagaries have combined to give these deformities an interest that even exceeds their clinical importance.

Three such cases have come to my attention. They combine so many unusual cardiac anomalies that their analysis embraces a large part of the field of cardiac embryology. By chance, they formed a series of defects, a new explanation for the mechanism of which was recently propounded by Spitzer¹ and discussed by Mönckeberg.²

REPORT OF CASES

CASE 1.—A colored boy, aged 14 months, was the youngest of five children. Parents and siblings were apparently normal. The child's birth and feeding were normal, but he had never been able to put on weight. In the last three months, he began to lose rapidly what weight he had attained. A persistent cough developed, and a daily afternoon fever was noted. In the last four weeks, a diarrhea of from four to five stools a day alternated with constipation.

The temperature was 103.6 F.; the pulse rate, 130. Moist râles were heard in both lungs. The cardiac apex impulse was in the right nipple line, but there were no murmurs, no cyanosis and no dyspnea. The abdomen was distended and tympanitic. The hemoglobin per cent was 80; the red blood cell count was 4,630,000

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* From the Department of Pathology of the Cook County Hospital.

1. Spitzer, Alexander: Ueber den Bauplan des normalen und missbildeten Herzens, *Virchows Arch. f. path. Anat.* **243**:83, 1923.

2. Mönckeberg, J. G.: Die Missbildungen des Herzens, in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2.

and the leukocyte count was 10,700, with 80 per cent polymorphonuclear cells. The result of the Pirquet test was negative. But the x-ray picture confirmed the clinical diagnosis of tuberculous bronchopneumonia and congenital dextrocardia.

At autopsy, the child was found to be severely emaciated. Though he had grown to a normal height of 68 cm., both anterior and posterior fontanel were still open and the teeth had not erupted. After the development of a fibrocaseous tuberculous primary lesion in the left upper pulmonary lobe and the caseation of the hilum lymph nodes draining the region, tuberculous cavities in the right lung had developed and an ulcerous ileitis. An acinose-nodose and miliary tuberculosis of both lungs terminated the case.



Fig. 1 (case 1).—Deformity of the heart viewed from the right. The letters indicate: *a*, rete Chiari; *b*, common auricular cavity; *c*, common atrioventricular; *d*, vestige of the auricular septum; *e*, left ventricle; *f*, ventricular septal defect, tricuspid valve leaflet and *h*, right ventricle.

No trace of the spleen nor of a splenic artery was found. The abdominal lymph nodes were enlarged to a diameter of 11 mm., and were discrete and reddish gray. Histologic examination of the nodes revealed numerous caseated tubercles with huge giant cells containing as many as a hundred nuclei. The liver showed a much larger left lobe than normal.

Heart.—The heart weighed 50 Gm. It lay with its apex in the right mid-clavicular line. It presented a large, common auricle leading through a common auriculoventricular opening into an incompletely divided ventricular chamber, which emptied through a single arterial trunk.

The large common auricle had a small right and a larger left auricular appendage. Its interior was crossed sagittally by a sparse network of fine fibers. This net began at the right margin of the coronary sinus, and inserted itself at the crista terminalis on the dorsocranial wall of the auricle. The pulmonic veins, which had united, opened by a single trunk just to the left of this insertion of the net, and the venae cavae to its right. No further semblance of an interauricular septum could be found, except a heavy muscular trabecula from 1 to 2 mm. thick. It stretched almost in the same plane as the net, across and just above the common auriculoventricular orifice.

This opening, 18 mm. in diameter, led into a large ventricular cavity. The cavity was divided incompletely and with marked inequality, by a rudimentary



Fig. 2 (case 1).—Deformity of the heart, viewed from the left. One may note the three semilunar cusps and the two coronary orifices. The letters indicate: *a*, single arterial trunk; *b*, hypertrophied left ventricle and *c*, bicuspid leaflet.

septum, into a large left ventricle and a small right one. The septum reached 12 mm., barely half its required height. Its concave upper edge thus left a gaping orifice 9 mm. in diameter between the ventricles. The insignificant right ventricle had a cavity from but 1 to 2 mm. wide, and was buried altogether beneath a large valve leaflet of the common auriculoventricular orifice.

Three leaflets guarded this opening. One originated from the entire right half of the auriculoventricular ring. It straddled the incomplete ventricular septum, covering the defect. It attached itself by three groups of chordae tendineae into the left ventricle side of the septum, and thus shut out the entire right ventricle.

No leaflets, at all, inserted themselves into the right ventricular cavity itself. A second, large one hung into the left ventricular cavity, and was attached by two groups of chordae into the posterior and left lateral walls. This leaflet was 14 mm. wide, and apparently was the most effective one in auriculoventricular closure. The ring was completed by a third small leaflet with a single group of chordae attached to the anterior wall of the left ventricle.

The enlarged left ventricle formed the apex of the heart. It formed practically the entire ventricular chamber. Internally it was 22 mm. in transverse, 18 mm. in anteroposterior and 22 mm. in longitudinal diameter. Its wall was 9 mm. thick. This large chamber opened by a single arterial trunk. From the left wall of the vessel, a small ridge extended into the anterocranial corner of the ventricular cavity. It reached in the line of the sulcus longitudinalis anterior toward the interventricular septum, and reduced somewhat the size of the defect of the latter. The large bicuspid auriculoventricular leaflet originated just to the left of this ridge.

No trace of a second arterial trunk was found. The single large vessel rested in the groove between the auricular appendages. It had three semilunar cusps, a left and a right each with a coronary orifice, and an anterior without. The coronary artery originating from the right sinus of Valsalva divided into a descending branch to the sulcus longitudinalis anterior, and a circumflex branch around the left side of the heart. Thus it really corresponded in distribution to the left coronary artery. That originating in the left sinus of Valsalva descended into the sulcus longitudinalis posterior. Thus it corresponded to the right coronary artery.

Two centimeters above the cusps, two vessels were given off. One directly supplied the left lung. The other promptly divided into an innominate artery and a vessel which led to the right lung. The left common carotid and subclavian arteries arose at a slightly higher level.

Summary.—The congenital defects in this case include:

- (1) Dextroversio cordis
- (2) Widely patent foramen secundum and primum atriorum, with absence of the septum secundum and spurium
- (3) Rete Chiari atriorum
- (4) Single pulmonary vein
- (5) Common auriculoventricular orifice with fusion of the tricuspid valve leaflets
- (6) Defective interventricular septum
- (7) Rudimentary right ventricle and hypertrophied left ventricle
- (8) Solitary truncus arteriosus aorticus with complete absence of the pulmonary artery
- (9) Detorsion defect of the truncus aorticus with reversal of the coronary arteries
- (10) Origin of the pulmonary arteries (left) from the aorta and (right) from the innominate artery
- (11) Aplasia of the spleen

CASE 2.—A white female infant had lived only to the age of 2 months. She was the youngest of nine children. The others were normal. This, the last child, for no apparent reason had failed to gain weight properly. She was dull and apathetic, and suffered from attacks of marked restlessness accompanied by a slight cyanosis and an occasional nosebleed.

Physical examination revealed poor nutrition, a bilateral coloboma of the iris and a mongoloid face. A slight cyanosis was noted, but no cardiac disturbances. The abdomen was distended. The liver, spleen and both kidneys were palpable. The hemoglobin per cent was 100, the erythrocyte count was 4,180,000 and the white blood cell count was 10,200, with 74 per cent polymorphonuclear cells. A trace of sugar and of albumin and many granular casts were found in the urine. The temperature rose terminally to 103.6 F., and a deep cyanosis developed.

Heart.—At autopsy (by Dr. R. H. Jaffé) the heart was in its normal position. It was somewhat larger than usual, but made up equally of both ventricles. It weighed 38 Gm., and was 50 mm. in transverse, and 45 mm. in longitudinal and in anteroposterior diameters.

When the heart was opened, two abnormal communications were found between the two chambers. One in the interauricular septum was oval, not valvelike, and

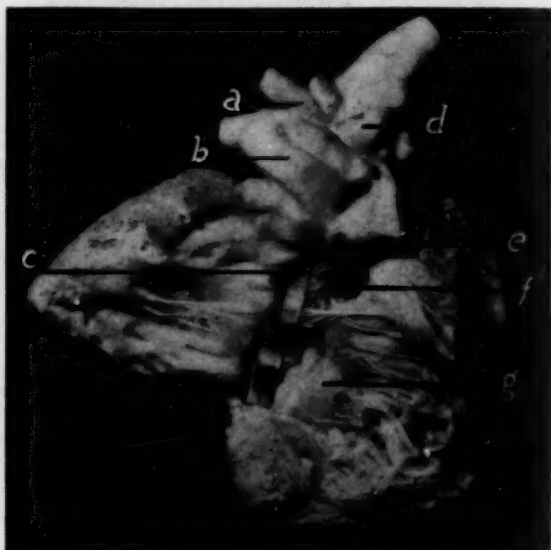


Fig. 3 (case 2).—The right ventricle. The letters indicate: *a*, aortic arch; *b*, right pulmonary artery; *c*, aortic valve; *d*, ductus Botalli; *e*, pulmonary valve; *f*, defect in septum and *g*, tricuspid valve.

about 3 by 5 mm. in diameter. It was located at the base of the septum 3 mm. from the mitral and tricuspid rings. Except for this intercommunication, the two atria were normal. The atrioventricular openings were also normal, the right 40 mm. in circumference, with three leaflets, the left 30 mm., with two.

The other defect was in the base of the interventricular septum, and was 7 by 8 mm. The two ventricles were of about the same size. The wall of the left ventricle was from 5 to 6 mm. thick; that of the right from 6 to 7 mm. thick. The left ventricle had no outlet except through the defect in the ventricular septum. Its vessel, the aorta, was found to originate entirely from the right ventricle.

Both the aorta and the pulmonary artery arose from the right conus. The aorta occupied a position posterior to but abnormally to the right of the pulmonary

artery. The aortic orifice was below the pulmonary valves, and separated from the septal defect by a fibrous fold 2 mm. thick. It was 5 by 7 mm. in diameter, and closed by two irregular cusps that did not appear to be adequate. The pulmonary orifice was larger, 9 by 10 mm. in diameter, and closed by three well developed cusps.

The aorta and the pulmonary artery were connected by a patent ductus arteriosus 5 mm. long, with an internal diameter of 4 mm. It opened into the aorta 23 mm. from its orifice and 5 mm. from the origin of the left subclavian artery. It started from the pulmonary arch, 10 mm. distal to its orifice, just anterior to the origin of the left pulmonary artery.

Only one coronary artery was present. It originated in the sulcus between the anterior aspect of the aorta and the pulmonary artery. It divided at once into two equal branches. One passed down the sulcus longitudinalis anterior to the



Fig. 4 (case 2).—The left ventricle. The letters indicate: *a*, aortic arch; *b*, left auricle and *c*, common coronary artery.

apex, the other passed to the right and posterior aspects of the heart. Thus it corresponded to the distribution of both coronary arteries.

Kidneys.—The other significant abnormalities were in the kidneys. These were larger than normal, the right weighing 24 Gm. and the left, 30 Gm. On both the external and the sectional surfaces of the cortex, many small, round, gray patches were just visible to the naked eye. An aberrant suprarenal gland, 3 mm. in diameter, rested in the hilum of the left kidney.

Histologic examination of the kidneys showed the numerous round gray patches to represent cysts. It offered a complete picture of the development of these cysts by gradual distention of the Bowman's spaces of the glomeruli, with compression atrophy of the capillary tufts. The cysts of the medulla seemed to have developed from the ducts.

No permission was granted for an examination of the head.

Summary.—The congenital defects in this case number:

- (1) Patent foramen ovale
- (2) Defect in the interventricular septum
- (3) Dextroposition of the aorta with complete origin of both arterial trunks from the right ventricle (detorsion defect)
- (4) Common coronary artery
- (5) Patent ductus arteriosus

(6) Hypertrophy of the right ventricle

Defects associated with the cardiac ones were:

- (7) Mongoloid idiocy
- (8) Bilateral coloboma of the iris
- (9) Polycystic kidneys

CASE 3.—A colored male infant, 5 weeks of age, was the second child of a healthy family, and had had a normal birth. Respiratory difficulty, relieved by rest, had been noted since birth. This was suddenly aggravated six hours before admission to the hospital. There were no convulsions, no cyanosis and no abnormal cardiac sounds.

No respiratory obstruction was found. The thymic area was wide to percussion. The pharynx was injected, and a few râles were heard posteriorly. The temperature was 97.6 F. Two days later, the child came to autopsy with a clinical diagnosis of thymic dyspnea or early bronchopneumonia.

The thymus was found to be of practically normal size, 8.5 Gm. No pneumonia, but a focal atelectasis of both lungs, was present.

Heart.—The essential abnormalities were in the heart. It weighed 41 Gm. and was markedly enlarged. It was 55 mm. in transverse, 45 mm. in anteroposterior and 50 mm. in longitudinal greatest diameters. It lay with its apex in normal right position, but was strikingly asymmetric. Externally, it could be seen that the sulcus longitudinalis, displaced to the right, separated a small right ventricle from a much larger left ventricle. The apex was formed entirely by the enlarged left ventricle.

The left ventricle was 20 mm. wide, 22 mm. deep and 30 mm. long in its internal diameters. Its wall was 7 mm. thick. The right ventricle measured only 14 by 16 by 24 mm. in the corresponding diameters. Its wall was only 2 to 3 mm. thick. The right and the left ventricles were separated by an interventricular septum 21 mm. high, which was incomplete in its upper portion, leaving an interventricular septal defect, 15 by 12 mm. in diameter.

Riding squarely over the septum and its defect was an enlarged pulmonary trunk. It had a circumference of 30 mm. and was closed by three semilunar cusps, a left, an anterior and a posterior. The left and right pulmonary branches were given off 7 mm. above the left and posterior cusps, respectively. The trunk then terminated in a widely patent ductus arteriosus. The ductus was 7 mm. long. It was funnel-shaped, so that its pulmonic end was 3.5 mm. in diameter and its aortic end only 2 mm. in diameter.

The aorta maintained an abnormal position anterior to and to the right of the pulmonic trunk. It issued from the right anterior corner of the right ventricle by a narrow orifice. Rather smaller than the pulmonic trunk, it had a circumference of only 18 mm. At the isthmus there was an abrupt narrowing to a circumference of 10 mm., but beyond the insertion of the ductus arteriosus, the aorta widened again to its original width. Just proximal to the isthmus, the innominate, the left common carotid and the left subclavian arteries were normally given off.

The aortic ring had three semilunar cusps, a right, an anterior and a posterior. From the posterior sinus of Valsalva sprang the right coronary artery running to the sulcus longitudinalis posterior. Thus the posterior cusp corresponded to a normal right one. Just to the left of and above the right coronary orifice, opposite the commissure between posterior and anterior cusps, was the orifice of the left coronary artery, which ran into the sulcus longitudinalis anterior. The anterior semilunar cusp thus corresponded to a normal left.

From the wall between the small aortic and the large pulmonic trunk, a short ridge extended into the ventricular chamber toward the antero cranial edge of the septum. This prolongation of the aortopulmonary septum toward the interventricular one closed part of the latter's defect. It reduced somewhat the communication between right ventricle and pulmonic trunk. The aortic trunk thus

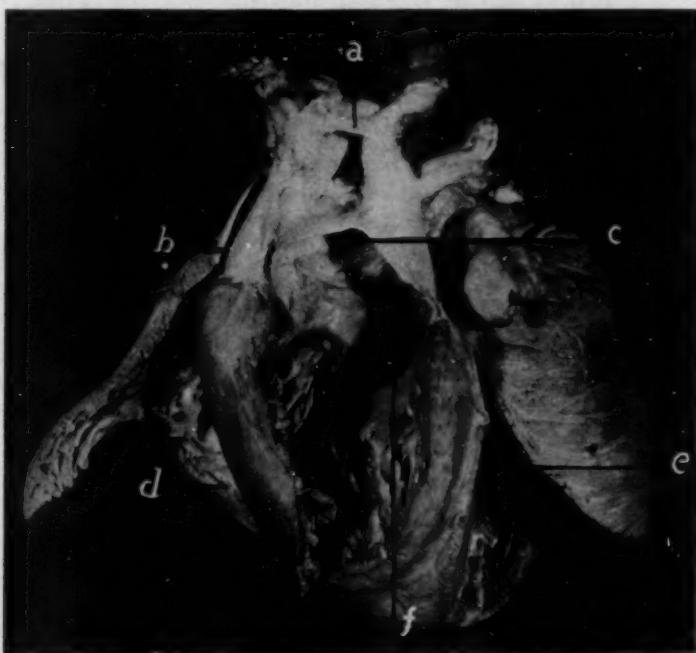


Fig. 5 (case 3).—Deformity of the heart viewed from in front. The letters indicate: *a*, ductus arteriosus; *b*, aorta; *c*, pulmonic trunk; *d*, right ventricle; *e*, left ventricle and *f*, defect of ventricular septum.

drained entirely from the right ventricle; the pulmonic from both, but mostly from the left ventricle.

The atria were normal, except that the left auricle was much larger than the right. The great venous trunks and the atrioventricular orifices were also normal.

Summary.—As congenital defects in this heart, there were, therefore:

- (1) Incomplete transposition of the great arterial trunks (detorsion defect)
- (2) Hypoplasia of the aortic trunk, especially at its isthmus
- (3) Patent ductus arteriosus
- (4) Interventricular septal defect
- (5) Hypertrophy and dilatation of the left cardiac chambers

ANALYSES

These arrays of cardiac abnormalities merit analysis, as far as recent conceptions of the mechanism of cardiac embryology can carry it. One separates from the changes secondary to intra-uterine endocarditis, those which, as in the present cases, arise from a primary deficiency in *vis a tergo*. There is a diffuse weakening in the growth vitality of various cell groups. These proceed lamely to form their appointed structures. They fall short of completion.

But, in this regard, one cannot consider the congenital defects as simple cessations of development. The congenital heart of a "blue" baby at term is not, for example, the heart of a normal fetus of the second month. For its various parts are growing at different speeds. And further, these primary delays in development give rise to such alterations of fetal cardiac physiology that the normal channels of growth are deflected from their course. Abnormalities arise, therefore, which have no counterpart in the normal heart or at best offer only a vague resemblance. Structures appear which should have completely involuted. Defects arise by failure of normal completion. Still other defects represent the secondary involution or the deflection of structures normally formed. All these must be sharply distinguished.

Decrease in growth vitality presumes some cause. This is to be found often in the exhaustion of multiple pregnancies. The first child was the last of a line of five; the second was the youngest of a line of nine children. All the previous children in each family were normal; the last ones were not quite fully equipped.

The deficiency is generalized. It is manifested not only in one organ, but here and there all over the body. The defects in the heart in the first case were accompanied by a complete aplasia of the spleen. Those in the heart in the second case were associated with polycystic kidneys, mongoloid idiocy and bilateral coloboma of the iris.

The heart in the human embryo of 2 mm. forms an unpaired tube suspended in its pericardial chamber. As it grows faster than the cavity in which it lies, it buckles to the right. It bends more and more until finally it bends into a complete circle in which the original caudal or atrial end comes to lie behind the original cephalic or bulbar end. With this bending, a complex longitudinal clockwise torsion takes place.

For the bending and the torsion, Spitzer¹ advanced this concept: In lung-breathing animals, according to him, the basis of cardiac development is the division of the organ into a double heart. In gill-breathing aquatic animals, the heart is single, with the respiratory and systemic parts lined up one behind the other, and with septums transverse to the stream. Terrestrial life and lung breathing bring a requirement for greater systemic energy and for an even far greater respiratory energy. The whole heart grows even beyond its original limits. It must therefore bend.

This increase in development is not uniform. The relatively greater respiratory energy required with lung breathing gives a relatively greater development to the pulmonary part of the cardiac tube. As it begins to compare with the systemic part, it lines up beside the latter, so that the two parts, instead of being one behind the other, are side by side.

The transverse septums melt under the increased force of blood flow. At first the systemic force is so much greater than the pulmonic that the two streams partly mix and septal development between the two parts of the heart is impaired. Such are the conditions of the incompletely divided hearts of amphibians and reptiles. With the relatively greater pulmonary development in mammals, the force of the pulmonic blood flow approaches that of the systemic. The streams no longer admix. Where they flow by each other, the pressure is least, and longitudinal septa are permitted to develop. When other factors disturb the equalization of pressure, septal defects develop.

The right side of the heart is separate from the left. Were it, however, a simple division, one side would be completely cut off from the other. Blood to the right side of the heart would be aerated by the lungs, and go in an endless cycle directly back to the right side. Blood to the left side of the heart would course through systemic channels and return unaerated to the left side, with never an exchange. Therefore, there must take place a complete, 180 degree torsion of the arterial end so that aerated pulmonary blood may go to the left side of the heart and be discharged therefrom, while nonaerated systemic blood goes to the right side of the heart and is discharged into the lungs. That such a rotation occurs is seen in the clockwise spiral of the aortopulmonary septum. Thus, in the definitive heart, as the pulmonic trunk descends it swings from behind the aorta around to the left and anterior, reversing, proximally, its distal relation to the aortic trunk.

On this theory, when the fetus is insufficiently endowed with vitality in vascular growth, these processes of cardiac development are not consummated. The pulmonic side usually suffers first and most. Normal development and normal involutions are impaired. Septal formation is defective. Torsion occurs incompletely or not at all, so that the so-called detorsion defects develop. The whole picture is finally clouded by the secondary changes arising from the alterations in fetal cardiac physiology.

In my first case, the single arterial trunk issuing from the hypertrophied left ventricle was guarded by an anterior, a right and a left semilunar cusp, whereas it should normally have presented a posterior, a right and a left cusp. That there had been a complete absence of the 180 degree clockwise spiral rotation was also proved by the reversal of position of the coronary arteries. That arising from the right cusp

corresponded in distribution to a normal left coronary artery. That arising from the left cusp had the normal distribution of a right coronary artery. One had here a complete, or 180 degree, detorsion defect.

I do not consider the single arterial trunk as a true, persistent truncus communis arteriosus. In the original truncus communis, four proximal endocardial buds develop. Fusion of the apposing larger pair forms the aortopulmonary septum. But in forming the septum, the pair of large buds is divided into four. These, with the undivided pair of small apposing buds, make a total of six, from which six semilunar cusps develop. If a single arterial trunk is really a persistent truncus communis, the proximal large pair of buds do not fuse. The septum fails to develop, and the buds are not divided. The single arterial ring is left with four endocardial swellings, to form four semilunar cusps. Thus von Huelse³ points out that a single arterial trunk may be considered a true truncus communis only if it has four semilunar cusps. Only two such cases have been described, one by Preisz⁴ and one more recently by Santa Cruz.⁵

If the large pair of endocardial swellings do fuse, the resulting septum divides the truncus into two vessels with six buds giving six semilunar cusps, three for the aorta and three for the pulmonary artery. This is the normal definitive state. But if the aortic or pulmonic side subsequently disappears, the single arterial trunk remaining would have only three semilunar cusps. Thus, if a single arterial trunk has only three cusps, it cannot be considered a true truncus communis. It must be held simply as a truncus solitarius, either an aorta or a pulmonary artery, with complete involution of its fellow.

That the single arterial trunk in my case¹ was an aorta is certified by the normal origin of both coronary arteries, as well as the great vessels of the head and upper extremities, from it. In cases of hypoplasia of the aorta, one or the other coronary artery has occasionally been described as found in the pulmonary trunk, but never both. In these cases, too, the pulmonic trunk continues into the descending aorta by way of a patent ductus arteriosus, and the great vessels of the head and arms have an anomalous origin.

In cases of single arterial trunk with three cusps, Mönckeberg² could find not even a histologic trace of a pulmonary artery. Von Huelse regarded these as cases of complete involution of the sixth (pulmonary) embryonic arch. The lungs are then supplied by bronchial arteries, by a persistent ductus arteriosus or by anomalous branches from the great vessels of the neck.

3. Von Huelse, cited by Monckeberg (footnote 2).

4. Preisz, cited by Abbott, Maude: *Osler's Modern Medicine*, Philadelphia, Lea & Febiger, 1925.

5. Santa Cruz, J. Z.: Common Ventricular Opening for Aorta and Pulmonary Artery, *J. Philippine Islands M. A.* 5:295 (Oct.) 1925.

The deficiency in the growth vitality of the pulmonary vascular elements reflected itself in several other abnormalities. The right or pulmonary ventricle was an insignificant vestige. The interventricular septum had been unable to reach its full height, and left a large interventricular defect above it. It was pushed over against the right lateral wall of the almost single ventricular cavity, and buried under the incompletely evolved tricuspid valve.

The auriculoventricular valves form, as do the semilunars, from four endocardial thickenings, two of which are split by the division of the heart. This gives six valve rudiments, each with a group of chordae tendineae. Normally, the left lateral and anterior buds, failing to divide, form the large bicuspid leaflet of the mitral valve with its two groups of chordae tendineae. A similar fusion occurred in my case between the left lateral and posterior buds to form the large leaflet that hung into the cavity of the left ventricle. But the whole tricuspid valve rudiment had also failed to divide. A single large leaflet with three groups of chordae remained on the right lateral wall of the ring. It represented all three of the tricuspid valve leaflets, and curtailed the entire right ventricle.

The completion of the ventricular septum was inhibited. Normally, it is effected by a union of the two large endocardial cushions at the base of the ventricle. This divides the auriculoventricular orifice into right and left parts. With this as a keystone, closure is consummated by a union with the septum primum atriorum growing down from above, with the interventricular septum growing up from below, and with the prolongation of the aortopulmonic septum extending backward from the anterior upper corner. This anterior portion was present in the anterior ridge described extending from the right wall of the single arterial trunk toward the ventricular septum. The presence of this trace of septum aortopulmonale is further proof for our contention that the original truncus communis had once been completely divided, and that the pulmonary side had involuted.

The large endocardial cushions, the keystone of the division, had failed altogether to develop. The interventricular septum had been unable to reach its usual height. The septum primum atriorum had not grown down far enough. Thus a large defect was left between the ventricles, and the auriculoventricular orifice remained undivided.

A similar retardation of development was suffered by the septum atriorum. The septum primum atriorum had developed. Normally, its inferior edge forms, with the endocardial cushions, a foramen primum, which is closed later by the completed growth of the septum. Absence of this closure left a persistent foramen primum. Normally, the septum primum then develops a large defect in its craniodorsal region, the foramen secundum or ovale. This is closed by the valvelike down-

growth of a septum secundum just to the right of the first septum. A large foramen ovale formed in my first case. It was denied closure, however, by the absence of a septum secundum. This reduced the interatrial septum to a narrow band stretching across and above the common auriculoventricular orifice, with a persistent foramen primum below and a large persistent foramen ovale above.

The network extending from the right margin of the coronary sinus to the crista terminalis, known as rete chiari,⁶ is the remains of the right valve of the sinus venosus. This valve definitely forms the thebesian and eustachian valves. It unites at the crista with the left valve of the sinus venosus to form the septum spurium. This left valve in my case was absent. Chiari's nets are not infrequent deformities.⁷ Twenty-six cases have been reported. Two other cases were but recently found by me in adult otherwise normal hearts.

The general decrease in the growth energy of the heart is seen also in the failure of the left atrium to take up the pulmonary vein in its wall. This vessel is absorbed normally until its second branching is reached. Thus four pulmonary veins come to enter the atrium. No such absorption occurred in my case; the pulmonary veins entered by a single venous trunk.

Clinically, a dextrocardia was diagnosed. The apex was on the right side. But one must distinguish between a situs inversus and a dextroversio cordis. The first represents a mirror image of the normal. The second is simply a shifting to the right of the cardiac apex. The normal left position of the heart is determined by two factors. First is the descent of the heart in the thorax. If this fails, as in ectopia cordis cervicalis, the apex is in the midline. Second is the upward growth of the predominant right lobe of the liver. This pushes the apex to the left. When the left lobe of the liver is abnormally relatively large, as it was in my case,¹ the cardiac apex is pushed to the right. Thus arose the dextroversio cordis.

Absence of the spleen was associated with a tremendous giant cell response in the tuberculous abdominal lymph nodes. Dr. R. H. Jaffé, in a personal communication to me, pointed out just such a response in animals which after splenectomy had been infected experimentally with tuberculosis.

The second case requires little additional comment. It comprises a somewhat less extensive congenital upset than the first. The common coronary artery represents a fusion of the right and left endocardial buds so that only two semilunar cusps remained to the aorta. The single coronary artery partook of the features of both vessels. It pos-

6. Chiari, H.: Net Formation in the Right Atrium of the Heart, Beitr. z. path. Anat. u. z. allg. Path. **22**:1, 1897.

7. Jordan, W. R.: Chiari's Network, Arch. Path. **2**:840 (Dec.) 1926.

sessed the anterior descending branch of the left, and the right circumflex branch of the right coronary artery.

Cases in which the aorta, somewhat dextroposed, rides over a ventricular septal defect, receiving blood from both ventricles, are not uncommon. Usually in these, there is an atresia or stenosis of the pulmonary artery as in Roeder's⁸ case and in Zimmermann's.⁹ Occasionally, the pulmonary artery is the main vessel, as it was in my third case. A complete dextroposition, however, with both trunks, separate and equal, arising entirely from the right ventricle is rare. The left ventricle can discharge its blood only through the interventricular septal defect.

Previously this defect was explained in the following fashion: With stenosis of one vessel or the other, septal defects arise, and the greater the stenosis the greater is the defect. Septal defects, unless small, cause such an alteration in pressure relations between the two chambers, that their normal developmental relations are altered. One enlarges at the expense of the other. In my second case, the right hypertrophied, and as it grew pushed the ventricular septum to the left. This left the aorta behind in the right ventricle.

Since in my case there was no stenosis of either trunk, it is simpler to apply Spitzer's detorsion theory. The aortic dextroposition would then represent simply a failure to complete the last stages of torsion. As the aorta in front and the pulmonary artery behind swung clockwise around each other to bring the latter anteriorly, the aorta had rotated posteriorly but not enough to the left to reach its appointed place in the left ventricle. Thus, the aorta instead of being, as it is normally, almost directly behind the pulmonary artery, was posterior but to its right. The clockwise torsion had not completed its 180 degrees, but only about 120 degrees. One had, then, in the second case, simply a 60 degree detorsion defect.

The aorta lagging behind in the far right corner of the right ventricle received but a part of the right ventricular discharge. The pulmonic trunk in its more central position close to the ventricular septum received, not only the rest of the blood of the right heart, but also most of the blood of the left ventricle, which was coming through the septal defect. This elevated the pulmonic pressure above the aortic, and kept the ductus arteriosus patent, to neutralize the difference.

As mentioned, cases of dextroposition of the aorta are not rare. The third case was, however, a direct reversal of such an anomaly. It was, in effect, a sinistroposition of the pulmonic trunk. The pulmonic artery had been shifted to the left and straddled the septum so that it

8. Roeder, O. J.: Complete Obliteration of the Pulmonary Artery, *J. A. M. A.* **79**:16 (July 1) 1922.

9. Zimmerman, H. M.: Truncus Arteriosus Communis, *Am. J. Path.* **3**:617 (Nov.) 1927.

belonged almost entirely to the left ventricle, but partly also to its proper ventricle, the right. The ventricular septal defect helped to maintain its communication with the right ventricle, but this was reduced by the prolongation of the septum aortopulmonale. This swung down from between the great trunks toward the ventricular septum to close the anterior corner of the defect. The aortic trunk was misplaced in the opposite direction. It was to the right of the pulmonic, and issued entirely from the right ventricle. Instead of being, as normally, posterior to the pulmonic trunk, it was anterior to it.

This almost complete reversal of the relative positions of the two trunks may be readily explained as the result of incomplete torsion. As the pulmonic and aortic trunks, the first directly behind the second, began to rotate clockwise around each other, they were stopped in the earliest stages. The pulmonic had moved a little to the left and anteriorly, the aortic a little to the right and posteriorly. About 60 degrees of torsion had been affected, and there torsion stopped, leaving each arterial trunk still in its wrong ventricle. One had then, in this case, a detorsion defect of about 120 degrees.

So one finds, in confirmation, that the semilunar cusps in each great trunk had shifted their positions part way around the circle. The pulmonic trunk should present an anterior, a right and a left cusp. In the case in question, it presented a left, an anterior and a posterior cusp. The aorta should have a posterior noncoronary and a right and a left coronary cusp; it had a right noncoronary and a posterior and an anterior coronary cusp.

The pulmonic trunk enlarged because it drained the entire left ventricle and part of the right. The aorta was hypoplastic because it received only part of the flow from the right ventricle. The pulmonic excess spilled over into the aorta by way of the funnel-shaped patent ductus arteriosus.

This third case stands between the first and the second. The first represented a detorsion defect of 180 degrees. In the second, torsion had been almost entirely completed, so that we had only a defect of 60 degrees. In the third, it had only been begun, giving a detorsion defect of 120 degrees.

CONCLUSIONS

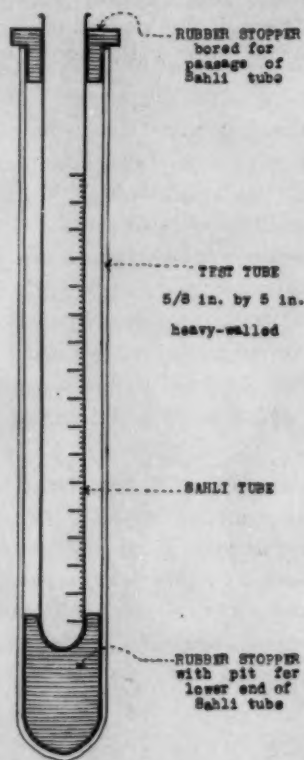
The puzzling picture presented by three cases of complex congenital cardiac anomalies have been analyzed as primarily based on detorsion defects. The three cases express different degrees of the anomaly. The first was a complete, the second a slight, and the third an intermediate, detorsion. Other defects were simply associated ones in the deficiency of vitality in vascular growth, or were secondary to the changes imposed by the detorsion.

Laboratory Methods and Technical Notes

A HANDY DOUBLE-PURPOSE HEMATOCRIT*

O. B. PRATT, M.D., AND H. O. SWARTOUT, M.S., LOS ANGELES

Having had frequent occasion recently to test blood both for the per cent by volume represented by the cells and for the carbon dioxide-combining power of the plasma we developed a simple piece of apparatus



Double-purpose device for testing blood.

which has proved very convenient. As it may at times be useful to others we describe it here.

For materials, one needs only a $\frac{5}{8}$ by 5 inch heavy-walled test tube, rubber stoppers and a graduated tube of the kind used in Sahli hemoglobinometers. The use of Sahli tubes for such a purpose is not a new idea, but we have not elsewhere seen a method of mounting similar to ours.

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* From the Research Laboratory of the White Memorial Hospital, College of Medical Evangelists.

The details of construction are shown in the accompanying diagram. The rubber stoppers are readily shaped with the aid of a cork borer and a pocket knife. The one in the bottom of the test tube fits snugly enough to prevent its falling out when the tube is inverted. The upper one is fitted water tight. The flange on this stopper prevents it from forcing itself down into the tube during centrifugation. The device does not need to be taken apart for cleaning, and we have been troubled but little with breakage.

We take blood by venipuncture, oxalate it and after careful mixing, pipet from 2 cc. to 2.5 cc. into the inner tube of each of a pair of these devices; we then centrifugate the preparation at high speed until there is no further noticeable diminution in the volume occupied by the cells. The upper levels of both cells and plasma are easily read on the scales of the Sahli tubes, the per cent by volume represented by the cells being calculated from the averages of the values thus obtained. The clear plasma is then pipetted off for use in the determination of its carbon dioxide-combining power in the regular way.

General Review

THE INTRACELLULAR "SYMBIONTS" AND THE "RICKETTSIAE" *

R. W. GLASER, D.Sc.

PRINCETON, N. J.

Certain investigators have been interested for years in the so-called intracellular "Symbionts" and "Rickettsiae," limited in their dispersion among vertebrates, but widely disseminated among invertebrates. In the latter animals, the micro-organisms are ordinarily regarded as innocuous parasites, commensals or true symbiotic forms, which live in a state of mutualism with their hosts. A symbiotic relationship is usually assumed, especially by workers on the more strictly biologic aspects of the subject. This attitude is founded principally on two generalizations: (1) the adaptation between the invertebrate and the invader has, in most cases, reached a marvelous degree of perfection, manifested by many morphologic and physiologic accommodations on the part of the host; and (2) the transmission of the micro-organisms to succeeding generations through the eggs of every individual of the species has been established in a remarkably orderly, though as yet unaccountable, manner.

Some of the micro-organisms in question, through the bites of their arachnid and insect hosts, gain an entrance into the vertebrate body, where they either are destroyed or manage to survive, although inhibited to such an extent that no injury results. Others appear to be adapted to the vertebrate as well as, or better than, to the invertebrate host, and cause serious diseases among men and domestic animals. In these cases of pathogenic effect, the parasites seem to be losing their perfect adaptation to the invertebrate host, for every individual of the species is not infected and, with one exception, transmission through the eggs has been abandoned. Neither the taxonomic status nor the food habits of the hosts can be correlated with the presence or absence of infection by "symbionts"; they occur within a great variety of totally unrelated forms, within blood-sucking and nonblood-sucking forms, within plant juice-sucking forms and within carnivorous, herbivorous, coprophagous and omnivorous species.

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* From the Department of Animal Pathology of the Rockefeller Institute for Medical Research.

It seems at this time advantageous to present a critical review for the purpose of assembling the most important matters, and to point out certain relationships and problems that have not been sufficiently emphasized. The literature on the intracellular "symbionts" and "rickettsiae" is extensive; for this reason, I may neglect a number of minor facts and points of view. Also a few papers remained inaccessible to me, and in these instances the citations of other authors have been accepted. Restriction will also be practiced for the sake of concentration on a circumscribed group of problems that appear interrelated. It is impossible at this time, for instance, to discuss fully the interesting relationships that exist between unicellular algae and certain protozoa, sponges, coelenterates and worms. It is also deemed advisable to omit a discussion of the interesting cecal bacteria of certain heteroptera described by Glasgow (1914), and the micro-organisms found in a peculiar organ situated in the connective tissue of certain operculate land mollusks, fully treated by Meyer (1925). The remarkable cases of extracellular symbiosis, as exemplified by Cleveland's work (1924, 1925) on the protozoa found within the alimentary tract of termites, will be only briefly treated because they do not appear to come within the scope of this review.

THE INTRACELLULAR "SYMBIONTS"¹ OF INVERTEBRATE ANIMALS

THE "PSEUDOVITELLUS" AND "SYMBIONTS" OF APHIDS

The subject of intracellular symbiosis in the higher invertebrates had its inception in an observation by Leydig (1850), who found green, yellow or brown granular masses within the blastoderm stages of certain viviparous aphid embryos. To Leydig, these masses appeared to lie free between the cells and later were converted into large spheres which became enveloped by membranes and participated in the development of the reproductive organs of the insects. Huxley (1858) described the structure in adult aphids and considered it an organ of inconstant form constructed of cells that enclosed yolklike spheres. To this author, the spheres were identical with the true egg yolk and he derived the fat body from them. Lubbock (1859) concurred with Huxley. Metschnikoff (1866), during his embryologic studies of *Aphis rosae* and *pelargoni*, had his attention attracted to a particular cell that occurred in the germinal invagination at the time of the formation of the blastoderm. This cell, which measured approximately

1. Portier (1918) and Meyer (1925) called attention to the fact that "symbiont" is a misnomer, the Greek word for "companion" or "partner" being "simbiote." Common usage, however, has soundly established the word "symbiont" unfortunately; so it will be retained throughout this discussion for the sake of preventing confusion.

0.013 mm. in diameter, contained, in contradistinction to the other cells, greenish or yellowish granules. It divided and formed a number of greenish or yellowish cells, which *en masse* separated from the remaining cells of the germ. Balbiani (1866) also studied the structure and found that the rapidly dividing cells formed a voluminous organ that remained in close proximity to the developing reproductive system of the embryo. This writer named the organ in question the "pseudovitellus," a name which has only recently been replaced by a more appropriate one (mycetoma or mycetome). Balbiani investigated the embryology of winter forms, in which phenomena occur somewhat different from those observed within the ova of viviparous females. He stated that within oviparous females a small follicular cell grows toward the ovum until the two touch; then a fusion occurs. The follicular cell, however, does not lose its identity, but becomes deeply embedded within the egg yolk, while anchored to the follicular epithelium by means of a delicate stalk. Later, the portal of entry into the blastoderm closes and the stalk is absorbed. Thus Balbiani traced the origin of the "pseudovitellus" in certain aphids. The observation, if correct, is remarkable, because it constitutes a case of the inheritance of certain characters through somatic cells. It is now well known that in many forms the "pseudovitellus" persists through embryologic development and with certain modifications maintains its identity even in the adult stage; but whether transmission of an entire somatic cell to the next generation occurs in aphids, in the manner described by Balbiani, remains in doubt. Subsequently, "pseudovitelli" were found at the posterior pole within the eggs of certain cicadidae, cercopidae, psyllidae, aleyrodidae, aphididae, coccidae, etc., by Heymons, Porta, Pierantoni, Sülc, Buchner and others. Pierantoni (1910) and Sülc (1910), independently, discovered that all these organs harbor micro-organisms that morphologically resemble in some cases either fungi or yeasts, in others bacteria.

Buchner (1912, 1919), Uichanco (1924) and Klevenhusen (1927) contributed many details in their studies of aphids that lead toward a better understanding of the "pseudovitellus" and its contents. Buchner designated the "pseudovitelli," "mycetomas" or "mycetomes," and the individual cells of which they are composed, "mycetocytes." The inhabitants of the mycetocytes were called "symbionts" by Buchner and all other recent workers. In the parthenogenetic form of the aphid *Macrosiphum tenaceti*,² Uichanco found two relatively large mycetomas in the abdomen. After birth the component units, or mycetocytes,

2. *Macrosiphum tenaceti* L. was used primarily because it belongs to Aphidinae, one of the most primitive subfamilies of Aphididae. Hence better prospects existed to observe characters that might otherwise be modified, obscured or lost as a result of specialization.

apparently cease dividing. They, nevertheless, increase in size from about 42 to 45 microns, in the first instar, to about 72 to 108 microns in the adult. After the insect has matured, these cells begin to degenerate slowly until the end of the aphid's life, when only a few remain. Buchner also found the cells of the mycetomas in *Drepanosiphum platanoides* large and possessing a correspondingly large nucleus, which usually contains a nucleolus. Both Buchner and Uichanco never found the nuclei invaded by the symbionts. Indeed, the immunity of the nucleus toward invasion has been observed by all workers in this field. In aphids, the cytoplasm of the mycetocytes is filled with large micro-organisms that resemble the yeastlike forms of certain fungi, but such heavily beset cells never show degenerative nuclear changes. It has always been a marvel to me that such cells, packed with foreign bodies, can exist at all. The symbionts themselves possess nuclei, and the figures of nuclear division have been observed in some of them. Fission, and not budding, represents the usual method of reproduction within the host. Variations in size of the fungi occur in separate mycetocytes; the round form investigated by Buchner measures between 2 and 4 microns in diameter. Occasionally, mycetocytes occur that do not possess a definite membrane. Such cells are in the act of discharging a portion of their inhabitants into the blood, where free individuals are sometimes found. Mycetomes and mycetocytes, with specific inhabitants, occur in every individual of a particular species of aphid whether amphigonous, male, female or parthenogenetic. A particular symbiont is always host-bound (exception: symbionts of mites); the same form is never found within different host species. Two or three distinct species of symbionts are, however, often found within one host. This universal infection is primarily due to the fact that transmission from generation to generation has been established through the eggs. Males also harbor mycetomas and mycetocytes with residents. The organs seem to bear a close topographic relationship to the testes, but entrance of the symbionts into the spermatocytes and spermatozoa has never been observed. For this reason, transmission of symbionts by the male is highly improbable. The transmission occurs only through the female, and in this manner simulates a sex-linked inherited character.

In viviparous aphid females, Buchner (1919) found that the egg prepares itself prior to infection. The posterior section of the blastoderm of the embryo separates from the rest and temporarily fuses with the surrounding follicle cells. At this time, the fungi are found within certain ovarian tubule mycetocytes. The surface of one of these mycetocytes dissolves and the fungi pass over into the specially prepared blastoderm cells. The invasion continues slowly and ceases when the embryonic cells mentioned have become entirely filled. Later.

the invagination of the germinal streak occurs at this point, and the fungi are carried into the interior of the embryo. The embryonic cells containing the symbionts constitute the embryonic "pseudovitellus" or mycetome. The foregoing interpretation by Buchner may be also the correct one for Balbiani's work, in which he derived the "pseudovitellus" from a follicular cell and described its passage into the egg of certain oviparous aphids.

In the parthenogenetic females of *Macrosiphum tanacetii*, and some other aphid species, Uichanco also found symbionts within certain cells of the ovarian follicular epithelium, where they multiply rapidly and produce some swelling of the follicle adjoining the posterior pole of the enclosed egg. The micro-organisms break through the thin epithelial cells and invade the posterior pole of the egg through a posterior opening in the periplasm. The vitellophags, which Uichanco now calls "mycetoblasts," are attracted to the micro-organisms and congregate around and between them in the posterior half of the egg cavity. This attraction of the "mycetoblasts" to the invaders simulates the behavior of leukocytes in the presence of foreign material (phagocytosis). The "mycetoblasts," together with the egg cytoplasm with which they are in syncytium, and the enclosed symbionts, form a subglobular mass. In this manner, the anlage of the "pseudovitellus" is established. Cellular differentiation of the anlage occurs after active mitotic division of the mycetocytes, shortly before the metameric segmentation of the germ band. After differentiation of the organ, the cells divide at least once during the embryonic stages of the aphid, increasing in number from about thirty or forty to about sixty or seventy. After birth, the cells do not divide and the entire organ measures approximately from 1 to 2 mm. in diameter. On birth, the organ is represented by a single mass of "mycetocytes," but later this mass divides into two lateral halves, apparently as a result of pressure exerted by the developing digestive tube. At about the fourth instar of the parthenogenetic female, the mycetome becomes reduced to isolated groups of two, three or more "mycetocytes," as a result of compression by the overcrowded and continually growing embryos within the mother. At this stage, the cells are larger, showing an increase from 42 or 45 to about 72 or 108 microns in diameter. The organs were found by Uichanco to be well supplied with large tracheoles.

Within oviparous females the situation varies again, as shown by Buchner for *Drepanosiphum platanoides*. After the nutritive nurse cell strands have been absorbed and the lumen of the ovarian tubule has closed anteriorly, separating the developing ovum from its successor, invasion by the fungi occurs. Individual fungi appear between the spaces in the follicle and the peritoneum, and are attracted by and penetrate the surface of the ovum, which invaginates a bit to receive

the invaders. The invasion of the ovum continues for some time, and the symbionts move anteriorly within it as if to make room for the succeeding individuals. The penetration of the fungi cannot alone account for all found within the ovum at this stage; active multiplication of the symbionts must also play a part. The wandering or invading forms appear slightly different from the resting forms within the mycetocytes of the adult. From the published figures, they seem longer, and many dividing individuals are evident. The fungi are later observed within the blastoderm, but the establishment of the embryonic mycetome of the oviparous female has not been traced. It apparently occurs in *Drepanosiphum platanoides* in a manner similar to that described by Buchner for the parthenogenetic females of the species, or to that described by Uichanco for *Macrosiphum tanacetii*.

Klevenhusen (1927) described cases of monosymbiosis, disymbiosis and trisymbiosis in aphids, or infection of the insects and their ova by one, two or three distinct micro-organisms. This writer suggests mechanisms to explain partially the sortings, migrations and orderly arrangements of the micro-organisms within the eggs and embryos. He finds that the relationships are simpler in the primitive aphids than in those more highly specialized. So-called primary symbionts are found in all aphids. These differ from host to host, but they are invariably round, are never degenerate and are located within mycetomes. These primary forms are considered the more ancient phylogenetically because they seem perfectly adapted to their hosts. The secondary forms often show degenerating individuals, and are elongated, rod-shaped or sausage-shaped. These are not so well localized and may occur free within the body cavity, within blood cells, connective tissue cells and œnocytes or within syncytial cell masses (primitive mycetomes or mycetocytes). Klevenhusen assumes that the secondary forms entered on the symbiotic relationship during more recent times, because their adaptation to the hosts is less marked than that of the primary forms.

THE MYCETOMAS³ AND SYMBIONTS OF THE CICADIDAE, CERCOPIDAE, PSYLLIDAE, ALEYRODIDAE AND COCCIDAE

Within *Cicada orni*, according to Buchner, conditions are complicated. This insect is disymbiotic, i.e., it possesses a mycetome and also unconcentrated mycetocytes that are really certain cells of the fat tissue. These mycetocytes harbor a totally different fungus from the one enclosed within the mycetome. This fat body fungus was named *Saccharomyces cicadarum* by Sülc, and although the lymph appears free the symbiont is capable of wandering around among the various fat

3. The term "mycetoma" or "mycetome" has now entirely replaced the older term "pseudovitellus."

cells. Some of these cells are filled with *Saccharomyces cicadarum*; others contain only three or four individuals. The mycetome of this insect is constructed of an epithelial outer layer of cells and an inner zone of morphologically different ones. A fungus occurs in the inner zone of cells immediately under the epithelial layer. This micro-organism has a totally different aspect from the one found within the fat cells.

Infection of the ovum begins after certain yolk preparations. The fungi enter the follicle and then invade the posterior pole of the ovum. At this point, masses of the fungus species derived from the mycetome accumulate with a few of the fat cell individuals. Within the ovum, after maturation, a distinct round mass is found composed of the two systematically distinct invaders, which segregate later during embryologic development and follow separate courses.

In *Aphrophora salicis*, another disymbiotic insect, belonging to the *Cercopidae*, a mycetome exists constructed of an outer and an inner group of mycetocytes. Two invaders occur within this mycetome; the peripheral cells contain one, which morphologically resembles a bacterium; the inner zone contains another having a fungus form. In the sexually mature insects, a few symbionts are found free in the lymph and in females are transported to the ova by this medium. The follicular epithelium is also infected with both forms, and when the invagination at the pole of the ovum ensues, the symbionts enter. The symbiont mass, containing the two species, appears, then, as a round ball in mature eggs. Buchner (1922) found that although both symbionts enter at the same time they remain segregated within this ball.

Much the same conditions exist in the larvae of *Psyllidae*, in which the mycetome occupies a large part of the abdomen and is constructed of a peripheral and an inner zone of cells, each zone harboring a distinct species of fungus.

In some of the larvae of *Aleyrodidae*, which are monosymbiotic, Buchner (1912) found a paired mycetome of a yellow, yellowish-brown or yellowish-red color, containing a single symbiont. In male pupae, the organ grows and wanders posteriorly toward the testes, which it completely surrounds. In females, in which the mycetome is much larger, a parallel phenomenon occurs. The architecture of the psyllid ovaries corresponds to that of the coccid ovaries. The oviduct has many side branches which bear the ova and their nurse cells. The nurse cells and ova are not differentiated as in other forms; both possess propagative characters; in other words, the nurse cells, often found in synapsis, are really oöcytes. The mycetome grows and moves posteriorly as in males; its mycetocytes invade the central portion of the ovary and everywhere fill the spaces between the fine ovarian tubes.

This is as far as the matter was traced by Buchner in 1912. Previously, Signoret (1867) had recorded that he found the yellow body within the ovum in later stages independent of the germinal streak. In 1919, Buchner resumed his observations on the aleurodids and discovered that entire mycetocytes with their residents wandered into the ova. These somatic cells maintained themselves a while before they lost their identity within the other embryonic cells. This observation is certainly suggestive of the one reported by Balbiani in 1866 for certain aphids.

In the coccids, which are also monosymbiotic, closed complexes or mycetomes are unknown. The fungi are found within certain fat cells and are transported around within the fat tissue and within the lymph. The invaded fat cells Buchner characterizes as facultative mycetocytes to distinguish them from cells that are obligatory, in other words, are predestined at an early stage to be used by the symbionts. Owing to the lack of restraint on the micro-organisms within the coccids, the former escape into the body fluids and may be encountered almost anywhere within the bodies of the insects. When the females mature, the fungi are found between the nurse cells and the ova. Each ovum invaginates at this point to receive the invaders and also emits protoplasmic processes which engulf them. Usually only a few symbionts, approximately fifteen, take part in this initial infection.

THE BACTERIOCYTES (MYCETOCYTES) AND BACTEROIDES (SYMBIONTS)
OF THE BLATTIDAE AND FORMICIDAE

Blochmann (1887) was the first to appreciate the significance of the bacteria-like structures within the tissues and eggs of certain insects. Wheeler (1889) also found and correctly interpreted similar structures within the egg of *Blatta germanica*. Cholodowsky (1891) agreed with the interpretations of Blochmann and Wheeler. The elements are often referred to in the literature as the bodies of Blochmann. Blochmann emphasized the resemblance between bacteria and the structures discovered by him, and in 1892 expressed the opinion that they bear a symbiotic relationship to the insects in which they are found. Later authors, Cuénot (1892), Henneguy (1904) and Prénant (1904), doubted the bacterial nature of the Blochmann bodies and referred to them as bacteroides. Blochmann found that in *Blatta* and *Periplaneta* the central portion of single fat cell groups is filled with straight or bent rods, from 6 to 8 microns long, which divide by fission. Such cells are entirely filled and do not contain any fat or urate bodies as is the case with the other cells of the fat body. The nuclei of these cells are never obscured and appear perfectly normal. In *Periplaneta orientalis*, these cells form a row and are surrounded by one-layered fat cells. In *Blatta germanica*, several rows of these bacteriocytes traverse the fat tissue.

Blochmann observed that transmission of the bacteria occurs from one generation to another. In *Blatta*, the young ova in the ovary are free; somewhat older ones show a few on their surface. The bacterial rods multiply with the growth of the ova, so that at first they form a single-layer, later a several-layered row around the periphery. Blochmann found the rods only rarely within the periplasm. In mature ova and in recently oviposited eggs, the layer is broken, so that it appears as if the multiplication of the rods cannot keep pace with the growth of the eggs. A direct wandering of the bacteroides out of the host cells toward the ova, through the follicle cells, was not observed. During the development of *Blatta germanica*, the rods lie under the blastoderm, after its formation, i.e., within the egg plasma. From here, they penetrate more deeply and collect in the spaces formed by the flowing together of the yolk. While this phase of embryonic development proceeds, the entoderm still persists on the ventral side of the egg. When this grows dorsally, the bacteroides are located only on the inner side of the ectodermal fat body. They fill certain cells that penetrate this tissue, thus presenting the typical picture found in the adult animal.

In 1892, Heymons published some work on four species belonging to the genera *Blatta*, *Periplaneta* and *Ectobia*. He observed that in *Blatta* masses of the rods collect in the middle of the ovum at the time when the germinal streak begins to overgrow the yolk. In *Ectobia*, the rods are more numerous than in *Blatta*, but at first they are also scattered on the surface of the ovum. After the beginning of the formation of the germinal streak all the rods concentrate in the middle of the yolk. Thus, in contradistinction to *Blatta*, the remaining parts of the ovum remain entirely free of bacteroides. In this manner, a large spherical mass appears, which is augmented by yolk cells or vitellophags.

For a species of *Periplaneta*, Buchner did not trace the events in detail. However, in 1912, he observed that the young oöcytes were free from infection. The larger ova showed each a number of rods at the surface, which were apparently derived from the bacteriocytes (mycetocytes) of the mother and must have wandered through the follicular membrane. Blochmann previously stated that he never saw the bacteria in the follicle cells of *Blatta germanica*. Buchner, however, found the bacteroides of *Periplaneta* not only extrafollicular, but also within the cells. As the ovum grows, the bacteria at the surface become much more numerous and form a closed layer around the periphery. A congregation of the micro-organisms composing this layer next appears at each pole and many rods are seen lying perpendicular to the surface of the ovum. According to Blochmann, the actual infection of the egg occurs late, since the bacteria first appear actually within the egg after oviposition. Buchner agrees with this view.

During the embryonic development of *Periplaneta*, Heymons observed the following facts: In young oviposited eggs, two principal bacterial concentrations are noticeable, one at each pole. The concentration at the posterior pole later shifts to a definite position at the posterior end of the germinal streak. At this place, the mass sinks into the yolk, and at the same time increases in volume owing to the multiplication of the vitellophags that invade the mass of micro-organisms. The nuclei of the invading vitellophags become larger than the nuclei of the outlying cells and divide amitotically. The whole concentration of bacteria and vitellophags migrates forward through the yolk and fuses with the anterior concentration. After the embryonic overgrowth of the yolk the mass is found within the middle intestine. The bacteria now disperse centrifugally and in scores move toward the intestinal wall, while the vitellophags degenerate. On reaching the intestinal wall, the micro-organisms penetrate the embryonic midintestine and reach the fat body where they enter certain cells, completely fill the cytoplasm of these, and consequently modify such cells morphologically and physiologically. In other words, they transform such cells into bacteriocytes.

From the outline presented, it is seen that in roaches infection from generation to generation is provided for by a series of definite events, apparently not as complicated as in some other cases, but interesting enough to stimulate even the most phlegmatic imagination. Many details in the chain of events are entirely lacking, and if known would undoubtedly assist much in the proper interpretation. However, a morphologic study, such as the one just described, can do no more than hint at underlying causes. How nonmotile elements are transported along definite, and in some cases, at least, rather sluggish, channels and find their way from the adult host cells to the immature ova and return is entirely unknown. One can postulate phagocytic and tropic reactions, as well as other things, between the bacteria and the various tissues involved; however, such speculations, while permissible and stimulating, do not constitute proof.

The situation in roaches is interesting from another aspect. These insects represent surviving members of an extraordinarily ancient group. Many extinct forms, with little change from the present ones, have been found in the carboniferous rocks. It would appear important to examine some paleozoic and mesozoic cockroaches, of which nearly 200 species have been described, in order to determine whether any evidences of former intracellular symbiosis or of actual parasitism exist. If such evidences survive, it would show the association to have already been established approximately 200,000,000 or 300,000,000 years ago, an important historical fact for parasitology and bacteriology. Paleontologists possess the necessary technic for making extremely thin

sections of fossilized material by a process of grinding, so that the determination outlined should certainly be attempted.

Among ants, Blochmann (1887) found that the early ova of *Camponotus ligniperda* and *Formica fusca* contained small rods. At first, the follicle cells are filled with the micro-organisms, but later they leave these cells and collect and multiply at the posterior vegetative pole of the egg. Blochmann also found the rods in female larvae of *Formica* and *Camponotus*; so there can be little doubt that the general condition simulates that found among the roaches. Ants have not been recently used as material for investigations on intracellular symbiosis.

THE MYCETOCYTES OR BACTERIOCYTES AND THEIR INHABITANTS WITHIN BLOOD-FEEDING FORMS

The intracellular symbionts of blood-sucking forms have attracted much attention within recent years owing to the fact that they either are identical with micro-organisms known as "Rickettsiae," or are often sufficiently similar, in many respects, to make a differential diagnosis impossible [Noguchi (1926) and others]. A group of workers placed certain intracellular inhabitants among the symbionts. Another group relegated others to the "rickettsiae" for wholly unnatural reasons. A separation of the intracellular yeast and fungus forms from the bacteria-like structures may be a perfectly natural taxonomic procedure, but why the intracellular bacteria-like micro-organisms found in arthropods are sometimes placed in the "rickettsia" group and at other times not admitted seems incomprehensible. The reasons underlying such a separation, on close analysis, do not hold, because, as stated, they are unnatural and a true classification is not built on convenience, but on phylogenetic relationships. Some workers place the intracellular invaders of the bedbug and louse, etc., among the symbionts; others place the identical micro-organisms among "rickettsiae." It must be recognized that the underlying biologic principles involved in these two artificial groupings are identical and that further progress in classification can only proceed by studying the detailed characteristics of the invaders and not solely the general reactions of the host. Are the pathogenic and nonpathogenic protozoa or the parasitic and nonparasitic nematodes classified as separate phyla, orders, families or genera almost exclusively because of size differences and on the effects they produce?

Since most of the literature on the intracellular symbionts has remained detached from that on the "rickettsiae," I have treated them separately. By so doing, I feel that I have been enabled to do greater justice to each group of workers and thus more properly to emphasize the close relationships that exist than would be possible by the handling of the two fields as a single entity. From the standpoint of conservatism, the method adopted may also be commended because should

it be proved later that one or more of the "rickettsiae" are not related to any of the intracellular symbionts, the whole subject will not have to be entirely disentangled again.

Work on the intracellular symbionts in blood-sucking forms probably had its inception in an observation by Schaudinn in 1904.⁴ This investigator found that species of *Culex* and *Anopheles* possess esophageal evaginations which are regularly filled with *Saccharomycetes*. The yeasts are also found within the midintestine of mosquitoes and, according to Schaudinn, are transmitted through the eggs. In 1914, Schaudinn thought that the yeasts aided the digestion of blood in mosquitoes and further attempted to show that the micro-organisms injected into the wounds by the insects, during the feeding act, were in reality directly responsible for the itching and for the subsequent development of wheals. Buchner (1922), however, also found and investigated the yeasts of mosquitoes, and showed that Schaudinn's conception concerning the pathologic effects of these micro-organisms was incorrect. Buchner discovered that he could obtain the same effect by subcutaneously or intradermally injecting into human beings extracts from mosquito tissues not containing the saccharomycetes; indeed, tissue extracts from species which do not suck blood and which do not harbor symbionts of any sort answered equally well. The phenomenon first investigated by Schaudinn is apparently a reaction produced by the toxic effects of insect proteins or their cleavage products.

Stuhlmann (1907) obtained some tsetse fly (*Glossina brevipalpis*) material from Koch and described symbionts that he considered protozoa in greatly enlarged cells of the midintestine. Roubaud (1919) studied the situation carefully and found that in the midintestine of *Glossina*, a zone exists in which the epithelial cells are from three to five times larger than their neighbors, extend far out into the lumen and form voluminous papillae. These special epithelial cells are filled with bacillary micro-organisms. The inhabitants or symbionts are liberated from time to time by the disintegration of the cells that enclose them, and can be found free within the intestinal lumen of all tsetse flies. The bacteria measure from 3 to 5 microns in length, are distinctly rod-shaped and often arched or flexed. Although the rods appear to multiply by transverse division, Roubaud thought that they were more closely related to the saccharomycetes because he also observed unequal division or budding. With this taxonomic interpretation, Buchner (1922) did not agree. The symbionts are found within the proventricular cells and within the intestinal lumen of the larvae of

4. Some observers claim that Koch first discovered intracellular micro-organisms in tsetse flies. Since no accurate account of this discovery has been recorded by Koch himself, I am inclined to think Schaudinn should receive priority.

Glossina, and were traced through the pupal stage to the adult. Roubaud did not with certainty find the symbionts within the eggs, but felt that they must be transmitted, because extremely young larvae are infected. This investigator also thought that the micro-organisms are in some way related to the physiology of digestion, and for this reason considered them symbiotic. Roubaud also recorded finding symbionts in other *Diptera*, namely, in *Lipoptena cervi* and in *Hippobosca equina*.

Buchner (1921, 1923) found a paired mycetome containing symbiotic bacteria in both sexes of the bedbug (*Cimex lectularia*). The organ is sharply circumscribed and oval, and occurs in the third abdominal segment to one side of the intestine near the reproductive organs. It is of the same color as the fat body and can readily be seen with a hand lens, measuring 5 mm. long by 3 mm. broad. The individual mycetocytes (bacteriocytes) are large polygonal, polynuclear cells, and their plasma is filled with rodlike micro-organisms and smaller round or oval bodies. On trituration, the mycetome reveals two types of rodlike bacteria. A few are thin, filamentous, motile rods, measuring from 3 to 7 microns long or longer; the others are shorter and non-motile, and appear to represent transition forms. Between all these rods, minute round or oval forms exist. These, as well as still other more highly refractive bodies, Buchner could not interpret. He also often encountered another bacterium-like micro-organism apparently distinct from the first. This was a thin, oval form, 3 microns in length, found within the mycetocytes, intestinal epithelium, fat, spermatocytes, nurse cells, germ cells, oviduct and receptaculum seminis. No injury results to bedbugs from their infection by any of the bacteria-like invaders.

The ovarian nurse cells become infected with the symbionts at an early stage. From these, they pass over into the immature ova with the secretory streams. Buchner, however, also found still earlier stages that as yet had no connection with nurse cells, infected. It seems, therefore, that the eggs of the bedbug receive their quota of symbionts in two days. This case is unique, for in all other recorded cases of symbiosis the ovarian nurse cells and nutritive secretory streams leading from them remain sterile.

In older ova, the symbionts congregate at the posterior end under the surface. During the formation of the blastoderm they infect some of the cells, and when the invagination of the germinal streak occurs, are found at the anterior end of this. Soon the infected cells and some of their parasite-free neighbors are separated from the epithelial layer of the germinal streak and the amniotic anlage. As aggregates of cells, they are forced anteriorly by the germinal streak, which is progressively sinking into the yolk. When the germinal streak bends

into the characteristic "S" shape, it also grows by these cell aggregates and leaves them behind. While this is proceeding, the symbionts multiply and form a definitely circumscribed mass enclosed within typical bacteriocytes. At this stage of development, the eggs of the bedbug are deposited. The mass then divides into halves forming two distinct organs or mycetomes, which sink into the region of the abdomen. The mycetomes increase in size with each instar. This does not depend on a multiplication of cells, but is caused by a progressive increase in the individual units due to several (from three to five) amitotically formed nuclei within each cell. The organs are well oxygenated through fine tracheae, which penetrate between the mycetocytes.

The first invader mentioned is also not entirely restricted to the mycetome and ovary. Buchner sometimes found the fat cells, the receptaculum seminis and the epithelium of the oviduct heavily infected. Conditions within the bedbug are complicated, and it is probable that several species of micro-organisms are involved. As will be shown later, the "rickettsiae school" apparently encountered similar difficulties.

Buchner (1923) also investigated another blood-sucking heteropteron, namely, the tropical conorhinid, *Triatoma megista*. In this insect, no mycetome was found, but rodlike bacteria were observed within the cells of the salivary glands. Within the parasitic larvae of *Gastrophilus equi*, however, a large mycetome richly supplied with tracheae was observed by this same writer (1922) in the posterior end of the body. This horse bot mycetome represents the largest one yet described, measuring 10 mm. long by 7 mm. broad. Its cells contain threadlike bacteria. The origin and development of the organ have not been studied, but in the sexually mature flies that do not feed, the organ is lacking. Hence, Buchner believed that a relation exists between parasitism by the fly and the presence of the organ. However, some of the symbionts must survive pupation in order to insure transmission to succeeding generations.

Sikora and Buchner independently (1919) discovered mycetomes and mycetocytes in lice. The genera *Pediculus* and *Phthirus* each possess an unpaired mycetome located within the midintestine on the ventral side. In *Pediculus humanis capitis* and in *Pediculus humanis corporis*, the human head louse and the human body louse, respectively, the mycetomes consist of small yellowish cell groups. These mycetomes are not in direct communication with the intestinal lumen, and the individual cells are inhabited by sausage-shaped and rod-shaped micro-organisms. *Haematopinus piliferus* is also endowed with an elongated organ near the intestine. Other species of *Haematopinus* studied do not harbor closed mycetomes, but possess single mycetocytes scattered over the entire midintestine embedded deeply between the

epithelial cells. The oviposited eggs of all lice contain symbionts located within the yolk at the posterior pole.

Miss Florence (1924) carefully studied the symbiont situation within *Haematopinus suis*, the hog louse, also previously investigated by Sikora, Buchner (1919) and Hindle (1921). She found the symbiont of the hog louse approximately 1 micron in width and showing great variety in length. The mean length for the shortest forms equals 2.5 microns. They are gram-negative and resemble rods, clubs, pot-hooks and crescents. Short chains or rod-shaped bacterial forms are always present. This observer found the symbionts present in the louse throughout its life history, located in mycetocytes on the wall of the midintestine. A well developed mycetome is found in each oviduct of the females. Miss Florence found that the symbionts were transmitted through the eggs. She felt that a physiologic relation exists between the symbionts and the digestion of blood, for the following reasons: 1. The mycetocytes are found in the midintestine where digestion occurs. 2. The increase of the symbionts is mechanically controlled through the rupture of the mycetocytes and the escape of the micro-organisms into the intestinal lumen. 3. Careful provision for transmission to the next generation occurs. 4. There is high mortality and an inability to raise a second generation when the lice are removed from their natural host and fed on man. As an appendix to the last statement, it may be mentioned that Miss Florence succeeded in a few instances in rearing lice until mature on human blood. In such lice, she was unable to find symbionts within the stomachs or within the eggs taken from the oviduct and uterus of the female. A second generation of lice could never be reared on human blood.

So far as the physiologic relationship between the digestion of hog's blood and the symbionts is concerned, the first fact observed by Miss Florence is suggestive, and the second one on the mechanical control of the micro-organisms may possibly be significant. The connection between points 3 and 4, however, I do not understand. Careful provision for transmission of micro-organisms to succeeding generations is provided for in all cases in which this curious relation between insects and lower forms exists. The micro-organisms are often, in many forms, far removed from the alimentary canal and any of its adnexa. The high mortality and inability experienced in raising hog lice on a foreign food is a phenomenon often experienced among other insects that do not harbor symbionts and are bound to a specific type of nutriment. The disappearance of symbionts from lice fed on human blood may simply signify that what has been experimentally proved to be injurious to the host is also injurious to the adapted invader. The same type of argument may really be applied to the first and second points also. The conditions within the mycetocytes located in the midintestine near the

digesting blood proved an ideal environment, and for this reason the micro-organisms settled there. That conditions are actually extremely favorable, under the louse's normal food conditions, is manifested by the continued development of the micro-organisms to such an extent that the host cells harboring them rupture periodically.

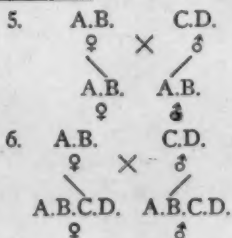
Intracellular invaders among the higher invertebrates are not restricted to insects alone, but have been described as occurring in ticks, mites, leeches and mollusks. Buchner (1922) discussed bacterial "symbionts" in ticks (*Ixodidae*). The species investigated by him did not possess closed organs or mycetomes, but mycetocytes within the malpighian tubules. The plasma of these cells is filled with large numbers of threadlike bacteria often compressed into masses. The micro-organisms appear within young oöcytes, in which they congregate in a definite zone. Thus, transmission to future generations is assured.

Reichenow (1921, 1922) found mycetomes harboring "symbionts" in two blood-sucking gamasids, namely, *Liponyssus saurorum* (a parasite of the lizard) and *L. musculi* (a parasite of the mouse). The mycetomes of the mites, three in number for each sex, border on the midintestine. Reichenow believed that the cells of the mycetome are derived from the intestinal epithelium and emphasized the close relationship between the micro-organisms and the digestive activities of the host. Reichenow often found two separate species of symbionts within the same species of mite, in other words, that disymbiotic relationships exist. More remarkable than this, however, is the fact, never observed in insects, that in separate individuals of the host species totally different invaders are often present dependent on the localities in which the mites were obtained. However, the descendants of a particular mite always harbor the same micro-organisms as the mother. Four distinct invaders are found. When two occur in one host, they are segregated in different cells and both occur within the three mycetomes to which reference has been made. The micro-organisms appear bacteria-like, often forming long threads, 57 microns long or less, which are coiled into spheres within the mycetocytes. The ova at a certain stage are ejected from the ovary and lie free in the body cavity in close proximity to the mycetomes. At this time, the transfer of the symbionts occurs, long before the eggs are enclosed within their uterine chorionic secretions. By the time the ova reach the uterus, two species of symbionts may be found within the yolk. When the nymph hatches, the intestinal epithelium and mycetomes are already formed. Reichenow did not follow the symbionts into the embryonic mycetomes.

Reichenow's observations on the invasion of the same species of mites in different localities by different symbionts is certainly interesting and may show that particular races of the host species must have remained rather isolated from one another. This, of course, can be

true only if the vertebrate hosts on whom the mites feed remained segregated. It may not be amiss to suggest, however, that perhaps the symbionts observed in different localities may be identical, except for racial or type differences produced by metabolic locality differences within the respective hosts. Indeed, Reichenow himself stated that a certain mite feeds on several distinct species of lizards. An attempt should be made to cultivate and study culturally, biochemically and serologically the various forms encountered. If cultures fail, light on the matter might be obtained by the experimental introduction of the symbionts from one locality into the same species of mites from another by crossing. Thus, a female harboring symbionts *A* and *B* from one place crossed with a male harboring symbionts *C* and *D* from another place would yield progeny, males and females, with symbionts *A* and *B* only, if, as in insects, the transmission is effected through the female to males and females.⁵ The result of such a cross would not signify much. If in mites, however, both sexes transmit symbionts, one would obtain all four of the micro-organisms within the offspring.⁶ If the micro-organisms are really distinct species, the two experimentally introduced forms will probably maintain their identity. If the four symbionts are not distinct but simply environmental forms, the host will soon reduce them to two forms. Of course, it must be determined that the new host does not violently react and destroy the foreign invader, but this supposition seems unreasonable because, in this case, the new and the former hosts are identical species.

Reichenow (1922) also found symbionts in the leech, *Placobdella catenigera*, a parasite of turtles. The esophageal glands of this leech are really mycetomes filled with bacteria-like forms. After the digestion of the blood has commenced, the micro-organisms are also found in the posterior end of the stomach. This, Reichenow believed, shows that they have an important digestive function. The author further made the general statement that bacteria are essential to all higher animal life and that in blood-sucking forms, or, in other words, in forms that feed on sterile food, bacterial contamination is provided for by the intracellular symbionts. It might, however, be well to call attention to the fact that Guyénot, Loeb and Northrop, Baumberger, Wollman, I and others have reared many generations of several species



of flies under absolutely sterile conditions. Furthermore, it is known with certainty that some of these insects in the wild state, and the same forms experimentally reared without micro-organisms or their byproducts, do not harbor intracellular symbionts.

Reichenow found all very young leeches infected with symbionts, so that he felt fairly confident that the invaders are transmitted from generation to generation. From his sections, however, he was unable to determine just when and how the transmission occurs.

A PRIMITIVE CASE OF INTRACELLULAR "SYMBIOSIS"

In all the cases of intracellular symbiosis discussed, the mechanisms evolved to assure transmission to succeeding generations are rather complicated. A simple and perhaps recent stage in the evolution of the curious association is exemplified in *Anobium paniceum*, a small beetle commonly occurring in flour, cereals, dried vegetables, etc. Escherich (1900) found certain cells in a section of the midintestine of all individuals of this species filled with yeasts undergoing active multiplication. Transmission to succeeding generations is assured, but the micro-organisms stick to the outside of the eggs; they do not enter them. The female eliminates the yeasts with the feces, and at the time of oviposition the chorion of the eggs becomes contaminated. On hatching, the larvae become infected as they gnaw their way out of the shell. Buchner later found that the yeasts survive the metamorphosis of the beetle by invading the imaginal disks.

HISTOLOGIC TECHNIC

Buchner (1923, 1925), Hertig and Wolbach (1924) and others have emphasized the difficulties encountered during the process of fixing, sectioning and staining material for studies on the intracellular symbionts and their relations to the host. Some of these difficulties are apparently those experienced by all workers requiring insects for histologic or microscopic purposes, and are usually due to the presence of chitin in the epidermal layer and tracheae, which prevents the proper penetration of fixatives and also causes further trouble during the sectioning process. With the exercise of patience and ingenuity, many workers have overcome these obstacles in one way or another. Nevertheless, the symbiont problems present a number of specific hindrances that are not so easily eliminated. Thus, Buchner observed that fixed and stained material is often confusing, and that whenever a heavy infection by symbionts occurs sections are frequently utterly hopeless. Either the micro-organisms do not stain at all, although the host tissues stain perfectly, or they and the tissues absorb the dye to such an extreme that nothing can be observed. If differentiation is then prac-

ticed, or if one decolorizes the symbionts to such an extent that one can actually observe some of the individuals and their structures, the host tissues will often be completely destained and orientation is impossible. This has frequently been my experience, as well as the experience of Buchner, and also of Hertig and Wolbach, who found that the symbionts of the bedbug stain poorly in sections. Investigators have therefore often been compelled to resort to a study of fresh tissues in conjunction with those histologically prepared. Much has been learned by macerating and triturating, in insect blood or in other isotonic fluids, excised ova, mycetomes or tissues containing individual mycetocytes. Often after such manipulations, the symbionts can be properly fixed and stained. Little can be learned in this way, however, concerning the embryologic phases, or the relationships of host and parasite.

If sections are prepared, they should be cut as thin as is practicable for a proper interpretation of the host tissues and their relations, and they may be stained with Heidenhain's or Delafield's iron hematoxylin, some counter dye, such as eosin or orange "G," being used. Fixation of the tissues may be effected with Petrunkevitch's mixture, or with Carnoy's, Flemming's or Bouin's fluid. Before fixation, various openings must be made in the body if the whole insect is used, and before it is embedded in paraffin most of the epidermal chitin should be removed. A method by Dahlgren (1898), combining paraffin and celloidin during the embedding process, proves extremely helpful in handling heavily chitinized material and prevents the tearing of the ribbons.

Specially prepared sections, at times, reveal both intracellular symbionts and mitochondria within the same cells. When the symbionts are rod-shaped, flexed or filamentous in form, as is often the case, the similarity between them and mitochondria may be pronounced. This fact has in the past caused much confusion. Some workers have considered mitochondria to be bacteria; others have identified the symbionts of blattids and ants as mitochondria. More recently, the former view has been generally extended by Portier, Meves and Wallin, who claim that mitochondria are in reality micro-organisms that symbiotically dwell within all animal and plant cells. Portier's views, when they first appeared, in 1918, created so much interest that in 1919 the Biological Society of France appointed a commission to test them. The experiments which were performed at the Pasteur Institute, showed that the so-called mitochondria cultivated by Portier from apparently sterile animal tissues were indeed bacteria that could be traced to contaminations. Wallin (1922) again revived the matter. His results were answered by the counter-experiments of Cowdry (1922), who showed that mitochondria presented totally different micro-chemical and

tinctorial properties from those of bacteria. Nevertheless, Wallin (1928) persisted in his views and published further experiments in their support.

So far as insect tissue is concerned, it can be stated that the intracellular symbionts and mitochondria are separate entities. When tissues are specially prepared and stained with Janus green, mitochondria are found within almost all cells. Under such conditions, the cells do not reveal the class of micro-organisms here discussed. When the tissues are prepared in another special manner, the symbionts are revealed and not the mitochondria. The micro-organisms are ordinarily restricted to particular organs or to isolated cells, whereas the mitochondria are universal. Lastly, cells infected with symbionts are usually packed with the invaders, little else being visible, except the nucleus. Mitochondria, on the other hand, do not completely fill the cytoplasm in this manner.

REACTIONS OF THE HOST TOWARD THE "SYMBIONTS"

The invertebrate host, although often apparently overwhelmed with symbionts, seems not to suffer any serious consequences. In other words, death of certain individuals directly traceable to infection by symbionts has not been recorded. Berlese (1906) estimated the number of fungi present in a single coccid, *Ceroplastes rusci*, to be between 60,000 and 70,000 cells. It is remarkable that in such forms as coccids and bedbugs, in which the blood distributes and generalizes the infection, no ill to the animals can be observed. These facts signify that the invaders and their activities may be inhibited or controlled to a certain extent; otherwise they would indefinitely multiply and destroy the host.

The mycetomes and mycetocytes show deformation of plasma, but the nucleus usually divides normally. The host is well adapted to its residents as evidenced by special receptor organs and cells, the mycetomes and mycetocytes, which are well tracheated. Complicated arrangements for transmission also exist and definite numbers of symbionts always enter the ova at identical places, usually at the posterior pole.

In spite of these adaptations, certain indications exist that point to a survival of more serious injury and to the former parasitic tendencies of the invaders. Developing mycetocytes often show an abnormal number of chromosomes. In coccids, 100 chromosomes exist in these cells, in contradistinction to twenty within the nuclei of the other somatic cells. Schrader (1920) also found that the mycetocytes of *Trialeurodes* possess double the number of chromosomes as the other somatic cells. Amitosis within the mycetocytes of *Periplaneta* is rather a common occurrence, and the tissues of *Cimex*

react by producing multinucleated giant cells. The nuclei of all infected cells become more heavily charged with chromatin, and fusions or agglutinations occur, forming large masses. The nucleoli also often multiply abnormally, and complete nuclear degeneration occurs at times. Indeed, in *Aleurodes* and in an African *Cicada*, Buchner at times observed complete dissolution of nuclei and their cells. Similar phenomena often occur in parasitic infections in other animals, and therefore the abnormalities observed in insects are suggestive. The facts mentioned are worth considering before one accepts the popular mutualistic view.

ATTEMPTS TO CULTIVATE THE INTRACELLULAR SYMBIONTS ON ARTIFICIAL MEDIUMS

The cultivation of many of the intracellular symbionts is highly desirable. Each real success would tend to dispel the notion, expressed by Cuénot, Prénant, Henneqy and others, that intracellular symbionts are products of cellular metabolism and not independent micro-organisms. It is, moreover, the only way in which it can be definitely established whether any particular host harbors one or several distinct invaders. In cases in which two or more morphologically distinct forms of fungi exist, the matter may not be so important. However, in the many cases in which invertebrates are found harboring bacteria-like, highly pleomorphic micro-organisms, often of small size, it is certainly important to know whether one is or is not confronted with separate species, or varieties, and whether a single species can be typed or not into separate races. This matter is important practically, for diagnostic purposes, in dealing with some of the pathogenic forms commonly known as "the rickettsiae."

By means of pure cultures, it will further become possible to study the enzymic or biologic activities of the symbionts, which may be correlated in some way with the metabolic activities of their hosts. Such investigations might possibly enlighten us on the question of mutualism.

Some investigators, in fact, have approached the subject from the cultural side, but in most cases the reported successes could not be verified and were invariably traced to contaminations. It is not strange that a group of highly adapted and specialized micro-organisms should present difficulties on artificial mediums. This obstacle can probably be overcome only through the application of special methods and specialized food and temperatures.

Schwartz (1924) believed that every reported success in the cultivation of the symbionts of aphids and scales can be traced to contaminations. Buchner (1925) more or less supported this view. Javelly (1914) and Hertig (1921) also pointed out the pitfalls into which those investigators fell, who described successes in cultivating the bacteroids of the blattids.

Blochmann (1887), Forbes (1892) and Lindner (1895) were among the first to attempt the cultivation of the intracellular symbionts, but were not successful. Successful reports have emanated from Moniez (1887), Escherich (1900), Berlese (1905), Conté and Faucheron (1907), Mercier (1906, 1907), Pierantoni (1910), Peklo (1916), Brues and Glaser (1921) and Schwartz (1924). However, on the basis of the criticisms made by Buchner, Javelly, Hertig and especially Schwartz, it is well to assume a sceptical attitude toward all reports of the cultivation of intracellular symbionts. Schwartz's work in 1924, however, because of its careful execution, seems worth recording in some detail. This investigator used seven species of scale insects of the genus *Coccus* (*Lecanium*), two members of the genus *Ceroplastes* and one of the genus *Pulvinaria*. Schwartz introduced the fungus symbionts, taken under sterile precautions from the insects, into moist chambers containing lymph or other special isotonic, well buffered mediums. Of 552 such cultures, only 6, or 1.1 per cent, showed any growth. Direct isolation of the symbionts from the insect on nutrient agar or gelatin was not possible. After the few successful "takes" had been obtained, it was possible to adapt the micro-organisms to other mediums and obtain luxuriant cultures. Single cell isolations were attempted, without success. Apparently, it is necessary to provide at least between ten and twenty cells in order to obtain a growth. In cultures, and within the insects, no spores or resting cells were observed. In insects artificially killed, the symbionts grew to long septated cells, which produced branchlike mycelia and died in from eight to fourteen days. Schwartz, therefore, believed that the invaders cannot survive the death of the host and lead a saprophytic existence. Schwartz studied the enzymic properties of four pure cultures of the fungus, as well as its carbon and nitrogen requirements. Since little is known concerning the metabolism of the host, the results with the symbionts must for the present remain indefinite. However, the author stated that if the host derives any benefit at all, it consists in the breaking down of the end-products of its metabolism by the fungi.

The reports of positive cultures in the literature hardly meet modern bacteriologic and mycologic standards. Schwartz's work is probably an exception, and the results reported by Escherich, Berlese and Brues and Glaser may be sound, but in the light of more recent experience these results require verification. In short, it cannot, to date, definitely be asserted that any micro-organism known as an intracellular symbiont has been cultivated outside the host body.

FURTHER REMARKS

It is clear from the preceding accounts that the phenomenon known as intracellular symbiosis is widespread among invertebrates and prob-

ably even more widely disseminated than indicated at present. It is interesting that this state of affairs, with certain modifications, arose in nature again and again in totally unrelated forms. This is no more nor less mysterious, however, than the frequent and independent appearance of true parasitism.

In 1920, I stated that the conditions now known as intracellular symbiosis had their origin in true parasitism, possibly in disease. The facultative and obligatory mycetocytes, and the closed complexes known as mycetomes, are often regarded as wonderful adaptations or residences furnished by altruistic hosts for the benefit of benevolent organisms of another type. Adaptations these structures are, it is true, but they undoubtedly represent what remains of former forts and other defense works and are not modern sanatoriums. In other words, the structures mentioned are survivals of previous profound pathologic changes or lesions, originally effected by vigorous and highly parasitic micro-organisms. That a balance has as yet not been perfectly established was emphasized with illustrations of abnormal numbers of chromosomes, amitosis, multinucleated giant cells and nuclear and cellular disintegration. As will be shown later, some of the micro-organisms involved in these changes are not showing the inevitable senile traits acquired by prolonged sojourns within benevolent cells, but are demonstrating extraordinary vigor by making excursions into the higher animals, in which they multiply actively, and incidentally create much suffering.

Buchner, Reichenow, Roubaud, Florence and others are not impressed with the hypothesis of parasitism. The phenomena also appear to them too orderly for a senseless commensalism, although the supposed benefits which the host and the invaders derive are admittedly by no means clear. The proximity of the micro-organisms to the alimentary canal in blood-feeding forms is considered evidence that a close physiologic relationship to nutrition exists. As pointed out previously, the micro-organisms probably settled where they did because of the presence there of favorable food, and not because their activities were essential to the well-being of the host.

Just how transmission through the egg became established is not known, but in the primitive case of *Anobium paniceum* we have one possible and suggestive step in the process. At any rate, the hosts reacted by gradually inhibiting the invaders to such an extent that the latter were rendered practically harmless. This defensive ability became heritable, but owing to the fact that an orderly transmission through the egg became established at the same time, the invaders could not be eliminated entirely. For these probable reasons, every individual of the species is infected today.

True symbiosis, or the association of plants, of animals and of animals with plants for reciprocal advantages is of rare occurrence

in nature. As discussed by Hertwig (1912) and by Wheeler (1923), social animals frequently not only gather and hold certain animals in bondage, but even protect and serve them, as in the interesting associations of ants with plant-lice, or even ants of other species. Such associations correspond rather to the domestication of animals, or to slavery, as practiced by man. The ants care for the plant-lice because of an evolved tropism (trophotaxis, trophobiosis) for the secreted honey dew, and steal the pupae of other ants and rear them, to use them later in their own service. This condition of affairs rests, consequently, not on equal rights, since the one animal, the ant, brings about the association, while the other is passively led into it.

An instance of most complete equal rights or true symbiosis is furnished by a hermit crab and an actinian, *Eupegurus pubescens* and *Epizoanthus americanus*. The hermit crab inhabits a snail-shell from the opening of which only his legs and pincers protrude. On this shell, an *epizoanthus* becomes attached and by budding soon covers it with a colony of polyps. The actinian is carried from place to place and shares the food which the crab captures. The polyps protect the crab with their nettle cells, while by growth they increase the size of the shell occupied by the hermit, thus saving him from constantly finding new abodes and from periodically exposing his soft abdomen to enemies. *Epizoanthus* undoubtedly began this mode of life as a parasite; indeed, it is really a parasite still, but since the association proves mutually beneficial it is regarded as a case of symbiosis. Through evolutionary adaptations, the association has undoubtedly been modified and improved.

Another case of true symbiosis is the interesting example elucidated by Cleveland (1924, 1925). It has long been known that termites harbor several large species of protozoa within their alimentary tracts. Cleveland discovered that he could defaunate the termites by incubating the insects, by starving them or by subjecting them to an atmosphere in which the oxygen tension had been raised. When such termites were so defaunated, they were no longer able to digest the cellulose in the wood on which they feed. Cleveland demonstrated that the protozoa are indispensable to the life of the termites. It is safe to conclude that the termite is likewise indispensable to the protozoa, because the symbiotic forms encountered are highly specialized and incapable of a free saprophytic existence.

Wheeler, in his studies on the relations of social to other insects, stated that symbiosis is probably never realized in its ideal form, unless we except the intraspecific relationships of such social animals as the termites, wasps, bees, ants and man. Symbiosis between separate species is rare in nature, as was shown, and when it does occur is by no means a perfectly evident reciprocity.

On the basis of this discussion, it seems best, therefore, to refrain from widely propagating the notion that the intracellular micro-organisms widely disseminated among insects are in mutualistic relations with their hosts. While such relations are within the realm of possibility, little proof for these contentions exists. Strong (1925) pointed out how in the tropics free-living saprophytic spirochetes often become parasitic through a commensal stage. It requires no great effort to imagine the passage of parasites through a commensal stage which at length terminates in symbiosis. However, proof of a state of symbiosis must be presented.

For years, *Hydra viridis* was supposed to live symbiotically with certain intracellular algae. As is now well known, some glycerine (0.5 to 1.5 per cent) was added to the culture water, the algae disappeared from the animals and the now colorless hydra lived perfectly well. Also, when certain protozoa and actinians that harbor algae are held in the dark, they become free of the invaders and proceed to live and reproduce normally. It may be possible to attack the problem of the supposed intracellular symbionts in a similar manner. In the case of *Anobium*, the chorion of the eggs can certainly be washed free of adhering yeasts. In other cases, Cleveland's technic or radiation might be tried. In large insects in which large mycetomes occur, excision of the organs might prove just as instructive as the castration practiced so successfully on a variety of insects.

Many other matters pertaining to the intracellular invaders require explanation. In leeches, mites, ticks, lice, bedbugs, tsetse flies, ants and blattids, the micro-organisms morphologically resemble bacteria; in cicadas, coccids, aphids and some other forms, they resemble yeasts and the higher fungi. Until most of these forms are artificially cultivated, little can be known concerning their true taxonomic position and biologic activities. Cultures will also settle the affinities of the forms found in cases of disymbiosis and trisymbiosis. Here lies an extensive field for entomologists interested in bacteriology and mycology.

What becomes of the micro-organisms when the host dies was answered for certain forms by Schwartz, who found that the invaders die, thus precluding a saprophytic existence for the species living today. This may, however, not be true in all cases.

The definite and orderly wanderings, or rather the passive transportations, of the micro-organisms within the bodies of their hosts is puzzling, especially when one remembers that nearly all the forms investigated are nonmotile. Transportation must be furnished in some way, but how? The invaders enter the egg at a prescribed place and in most cases follow definite routes until they locate within the mycetocytes and mycetomes. Later, when the animal matures, they again follow definite channels until the eggs are reached and no egg

escapes infection. In disymbiotic animals, sometimes both forms enter in a mixed condition. We are almost entirely ignorant of the factors that separate them and permit one to go to certain fat body mycetocytes and the other to form a mycetome. Within the eggs, transportation by the vitellophags is possibly often furnished, and within embryos migrating and shifting cells may constantly provide the necessary energy. After birth, the phagocytes and lymph also probably play a decided rôle. No definite knowledge, however, exists about these matters.

When did the relationships discussed first originate? As previously suggested, an examination of certain fossil arthropods might shed some light on this matter.

I have criticized the symbiotic hypothesis, but am inconsistent and retain the old terminology. This is a conservative and convenient procedure; conservative, because it is not certain that some of the micro-organisms are not symbionts, and I merely caution against the surety with which they have been pronounced such; convenient, because workers everywhere use the words "symbiont" or "symbiote" freely and a change to, for instance, "mild parasite" or "harmless commensal" might produce more confusion. Experiments may finally settle the terminology as well as solve some of the problems involved.

(To be concluded)

Notes and News

University News, Promotions, Resignations, Appointments, Deaths.—

On December 9 the graduates of the school of medicine of the University of Michigan presented to the university a portrait of Frederick G. Novy, professor of bacteriology and director of the hygienic laboratory, in celebration of his sixty-fifth birthday. Doctor Novy has been a member of the medical faculty of the university for forty-three years.

The Philadelphia Pathological Society has awarded the Gerhart medal to Eugene L. Opie, professor of pathology in the University of Pennsylvania.

William F. Petersen, Chicago, and Karl V. Weller, Ann Arbor, Mich., are president and secretary, respectively, of the American Society of Experimental Pathology, the next meeting of which will be held in Chicago in 1930.

Kenneth N. Lynch, professor of pathology in the medical college of South Carolina, has been elected president of the American Society of Tropical Medicine.

Joshiki Morishita, assistant in bacteriology at Yale University and engaged in the study of dental bacteriology and pathology, has died at the age of 33 years.

At Columbia University, New York, Hans Smetana has been appointed assistant professor of pathology, and Claus W. Jungeblut associate professor of bacteriology.

New Department for Research in the Toledo Hospital.—This department, which is built in association with the new hospital, occupies 60,000 cubic feet of space and contains laboratories and rooms for animals. Adequate facilities are provided for local physicians who wish to do experimental work.

Brown Orthopedic Research Fellowships.—These fellowships, the income of which is \$2,400 a year, are open to physicians and surgeons throughout the country, regardless of race, creed or color. Two fellowships are awarded each year not later than December 25. For particulars address the Director, Hospital for Joint Diseases, Madison Avenue and 124th Street, New York.

Permanent Science Fund.—This is a new fund for advancing scientific research. As trustee of the Permanent Science Fund, the Boston Safe Deposit and Trust Company will receive in trust gifts and bequests. The income will be paid over to the American Academy of Arts and Sciences for disbursement in the aid of scientific research. Applications for grants-in-aid should be addressed to the committee on the Permanent Science Fund, 28 Newbury Street, Boston.

Blood Grouping.—Under the leadership of Dr. T. Madsen, president of the committee of hygiene of the League of Nations, and with the collaboration of leading serologists in a number of different countries, including the United States, the test serums, Anti A (group 3) and Anti B (group 2), are being standardized, no doubt with the purpose of recommending the use of a high-titered serum of definite strength in carrying out the blood groupings previous to transfusion. This plan of using high-titered serums for the groupings has already been followed in a rough way by some institutions. The Cooperative Blood Donors' Bureau, which was established in New York City last year under the auspices of the committee on blood grouping of the National Research Council, is supplying such serums, which are capable of clumping an equal volume of the respective corpuscles on the slide in five seconds. Only a relatively small percentage of persons of the two groups possess such active serum. The use of these standard serums will greatly shorten the time necessary for grouping blood and will lessen the number of mistakes made in this test.

Obituary

HARRY TAYLOR MARSHALL, M.D.,

1875-1929

Harry Taylor Marshall, Walter Reed professor of pathology and bacteriology in the University of Virginia, died on Nov. 8, 1929, in Paris. He was born in Baltimore, May 19, 1875. His father, Charles Marshall, was biographer and chief of staff of General Robert E. Lee. He secured the A.B. degree from Johns Hopkins University in 1894 and the M.D. degree four years later. He was intern in the Johns Hopkins Hospital, fellow and later assistant in pathology, and from 1903 to 1906 instructor in medicine and pathology in the Johns Hopkins School of Medicine. During 1903 and 1904 he served also as professor of pathology in the Baltimore Medical College. The year 1901 to 1902 he spent with Paul Erlich in Frankfort-on-Main on a traveling fellowship from the Rockefeller Institute. In the autumn of 1903 and the summer of 1904, he worked in Montana on the loco-weed disease of cattle as special pathologist for the United States Department of Agriculture. The results of these studies are summarized in volume 25 of the *Bulletin of the Johns Hopkins Hospital*. In 1906, he was appointed professor of pathology in the University of the Philippines, and at the same time he served also as pathologist to the Bureau of Science and for one year as secretary and registrar of the College of Medicine, Manila. He returned in 1908 to accept the Walter Reed professorship of pathology and bacteriology in the University of Virginia, where he remained the rest of his life.

He was a member of the Virginia Tuberculosis Commission from 1915 to 1918, and during the last two years he served as director. He was a member of the Virginia State Board of Health from 1916 to 1924. He was president of the American Association of Pathologists and Bacteriologists in 1922, chairman of the section on pathology of the Southern Medical Association in 1928 and secretary in 1929.

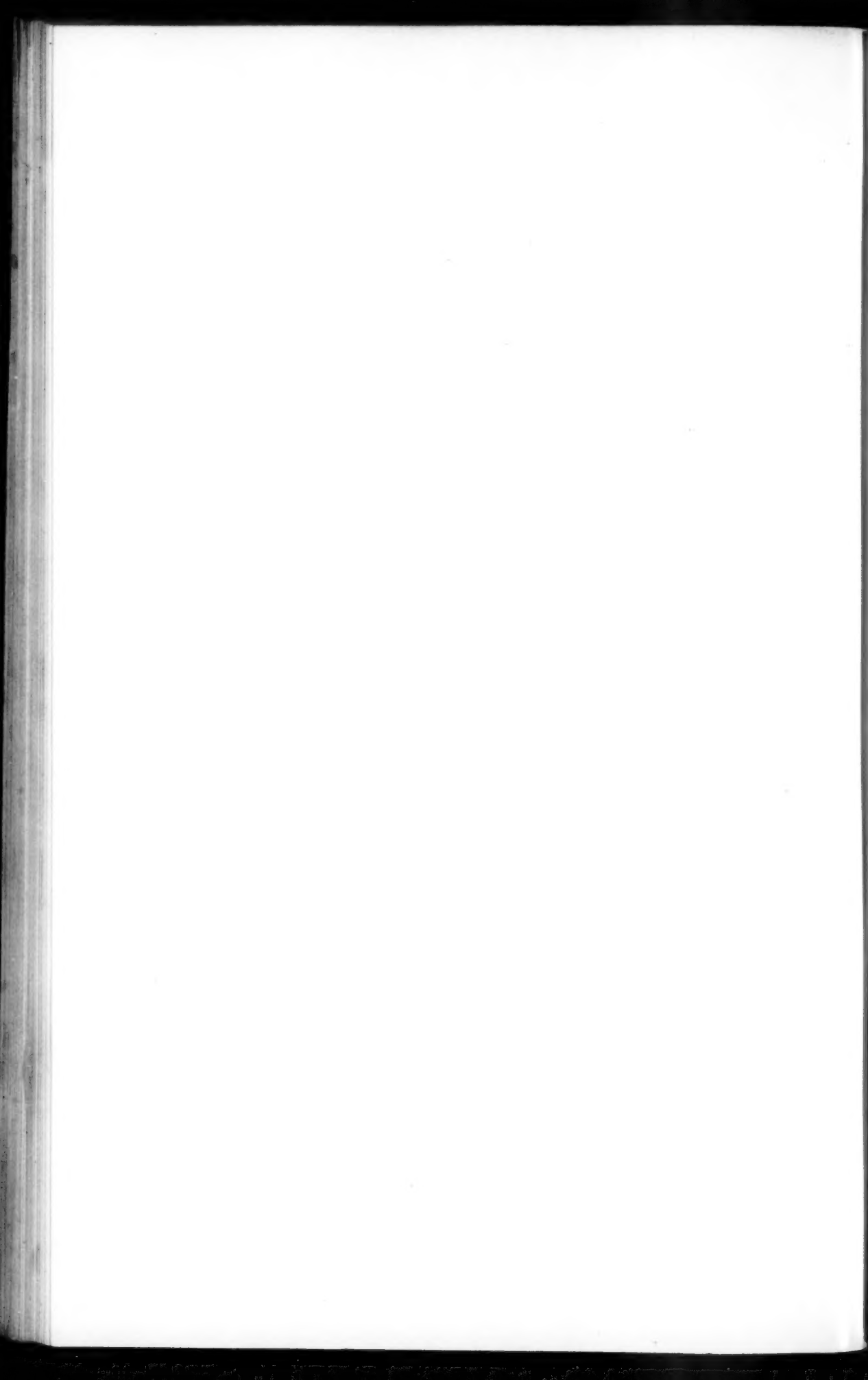
Dr. Marshall gave himself unsparingly to every cause that seemed to him to be worthy of his efforts, and his death is a great loss.

H. E. JORDAN.



HARRY TAYLOR MARSHALL
1875-1929





Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE AGING OF HEART MUSCLE. ALFRED E. COHN, *Am. J. M. Sc.* **177**:619, 1929.

Old age is discussed from a biologic point of view and various theories are presented. Certain diseases appear to depend for their explanation on the processes of growth rather than on accidents dependent on the external environment. In the light of these theories, certain cardiac maladies in which pain is a prominent complaint and which occur in advanced years take on a new and different meaning, not only in the comprehension of their pathogenesis, but also in the provision for their relief.

PEARL ZEEK.

ASTHMA AND THE VAGAL INNERVATION TO THE BRONCHI. HARRY T. R. MOUNT, *Am. J. M. Sc.* **177**:697, 1929.

Stimulation of the vagi in animals often produces changes in the lungs, such as bronchial constriction, bronchorrhea, cellular infiltration and emphysema, similar to those seen in asthma. In the dog, the fibers involved can be sectioned without untoward symptoms. These experiments suggest a procedure that might be considered in certain cases of asthma.

PEARL ZEEK.

THE PANCREATIC TRIAD. W. N. BOLDYREFF, *Am. J. M. Sc.* **177**:778, 1929.

Complete loss of pancreatic fluid, either through pancreatectomy or fistulae, produces a "pancreatic triad" of: (1) rise in the percentage of blood sugar, (2) decrease of the blood coagulability and (3) leukocytosis.

PEARL ZEEK.

INCREASE IN BLOOD SUGAR FOLLOWING THE INGESTION OF GLYCEROL. JULIUS FERBER and SOPHIE RABINOWITSCH, *Am. J. Med. Sc.* **177**:827, 1929.

Glycerol given to a human being on an empty stomach will produce hyperglycemia. The extent of the hyperglycemia is in direct ratio to the disturbance of carbohydrate metabolism of the particular person. In the more progressive cases of diabetes, the glycerol may produce glycosuria, as well as hyperglycemia. These facts warrant the conclusion that in the human body, glycerol is converted into dextrose.

AUTHORS' SUMMARY.

SYSTEMIC HISTAMINE-LIKE REACTIONS IN ALLERGY DUE TO COLD. BAYARD T. HORTON and GEORGE E. BROWN, *Am. J. M. Sc.* **178**:191, 1929.

Six cases are reported in which local and general symptoms of cold allergy were exhibited. The local effects on the skin were: pallor during the period of exposure, and subsequent redness, swelling and increased heat of the hands after removal from the cold. A characteristic systemic reaction appeared, following a latent period of from three to four minutes, which was characteristic of that produced by histamine. There was a fall in blood pressure, a sharp rise in pulse rate, flushing of the face, a tendency to syncope, with transitory recovery in from fifteen to thirty minutes. Complete recovery from the local reaction occurred in from twelve to twenty-four hours. The experimental work which was carried out gave evidence of the chemical nature of these reactions, and strongly suggested the release of a histamine-like substance in the skin following exposure to cold; this substance, when carried in the general circulation, produced a reaction characteristic of histamine. These cases are amenable to treatment. By daily immersion of the hands in cold water, decreasing in temperature, for increasing periods,

excellent results may be obtained. These clinical observations are further confirmation of the work of Lewis and his associates on the presence of histamine or allied substances in the skin of human beings.

AUTHORS' SUMMARY.

FAMILIAL GLYCOSURIA: REPORT OF A LARGE FAMILY. H. M. BABCOCK, *Ann. Int. Med.* **2**:923, 1929.

Eighteen members of one family (representing 58 per cent of the persons studied) were found to have a reducing substance in the urine in the absence of other symptoms or signs of diabetes mellitus. The glycosuria was present in four generations.

WALTER M. SIMPSON.

BASAL METABOLISM IN POLYCYTHEMIA VERA. T. L. BLISS, *Ann. Int. Med.* **2**:1155, 1929.

Of twenty-three patients with polycythemia vera, 15 (65 per cent) showed an increase of the basal metabolism rate above the normal range of plus 10 per cent. There is no constant relationship between the basal metabolism rate and the increase in blood volume, the cell volume, the erythrocyte count or the concentration of hemoglobin.

WALTER M. SIMPSON.

THE INEFFECTIVENESS OF HIGH DOSES OF IRON IN CURING ANEMIA IN THE RAT. J. WADDELL, H. STEENBOCK and E. B. HART, *J. Biol. Chem.* **83**:243, 1929.

Iron salts which have been carefully purified from contaminations of copper salt are ineffective for the correction of the anemia induced in young rats by maintenance on a milk diet.

ARTHUR LOCKE.

FURTHER PROOF THAT THE ANEMIA PRODUCED ON DIETS OF WHOLE MILK AND IRON IS DUE TO A DEFICIENCY OF COPPER. J. WADDELL, H. STEENBOCK, C. A. ELVEHJEM and E. B. HART, *J. Biol. Chem.* **83**:251, 1929.

Young rats which have become anemic after maintenance on a diet of whole milk and iron show an equally rapid return to the normal after the addition to their ration of liver, liver extract, liver ash, the copper-containing fraction of that ash or equivalent preparations of copper sulfate. "This is additional and convincing proof that the deficiency of this basal diet is *inorganic* in nature and that this inorganic deficiency is copper only."

ARTHUR LOCKE.

THE EFFECT OF AVITAMINOSIS ON HEMATOPOIETIC FUNCTION. B. SURE, M. C. KIK and D. J. WALKER, *J. Biol. Chem.* **83**:375, 387 and 401, 1929.

There is no relation between vitamin A deficiency and pernicious anemia. Deficiency of either vitamin A or vitamin B may be reflected in a slight initial anemia, followed by a later increase in the red cell count, which is occasioned by the associated anhydremia. Vitamin E appears to be without effect on the hematopoietic function.

ARTHUR LOCKE.

EFFECT OF HISTAMINE AND OF LOCAL INJURY ON THE BLOOD VESSELS OF THE FROG. R. T. GRANT and T. DUCKETT JONES, *Heart* **14**:339, 1929.

Local injury to minute vessels of the frog's tongue causes (a) a local and active dilatation independent of the nervous system and (b) a surrounding secondary dilatation dependent on the integrity of a local nervous mechanism and corresponding to the "flare" of the human reactions. The local reaction is caused not by direct injury to blood vessels but to some chemical substance released from the damaged tissues. In the human being, this substance is probably histamine. However, histamine causes no dilatation of the frog's blood vessels, either when

applied locally or given intravenously. The effect in the frog is probably due to a base of the histidine-arginine fraction from skin extracts of the animal.

PEARL ZEEK.

EFFECT OF ERGOSTEROL ON THE AORTA OF RABBITS. R. MANCKE, Arch. f. exper. Path. u. Pharmacol. **141**:228, 1929.

On addition of irradiated ergosterol to the food of rabbits, marked calcification of the aorta with aneurysmal dilatation resulted regularly.

THYROID GLAND IN PREGNANCY AND THE REACTION OF REID-HUNT. R. BRUEHL, Klin. Wchnschr. **8**:254, 1929.

The resistance of mice against acetonitril poisoning is increased, not only after feeding thyroid substance, but also after giving blood taken from cases of hyperthyroidism. An increased thyroid function in pregnancy is generally accepted.

The blood from pregnant women was given to mice by mouth and later by subcutaneous injection, and the reaction of Reid-Hunt was determined in the animals. No substances which increase the resistance of mice against acetonitril poisoning could be demonstrated in the blood of pregnant women.

Therefore, an increased thyroid function in pregnancy is questioned, in spite of the enlarged thyroid gland, the elevated basal metabolism and the high level of iodine in the blood in pregnant women.

C. A. HELLWIG.

THE FUNCTIONS OF THE STOMACH IN HEART AND KIDNEY DISEASES. J. FLIEDERBAUM and N. PIANKO, Klin. Wchnschr. **8**:1076, 1929.

Diseases of the heart and kidneys without edema and uremia are not associated with variation of the stomach function. When kidney insufficiency is associated with increased blood urea there is often an increased excretion of urea by the stomach. With cardiac and renal edema, the acidity and the chloride content of the gastric secretion are diminished and the excretion of neutral red after its injection into muscles is delayed. These disturbances do not occur when the edema is caused by local ulcerations. The variations in stomach function are independent of the intensity of the lesions of the heart and kidneys. They are parallel with the edema of the skin, the dryness of the mouth and with the oliguria. These may precede the appearance of the edema, and the results justify the conclusion that extrarenal factors are important in the origin of edema, as stated by Volhard.

AUTHORS' SUMMARY.

THE RHYTHMIC FUNCTION OF THE LIVER AND ITS SIGNIFICANCE FOR CARBOHYDRATE METABOLISM IN DIABETES AND INSULIN TREATMENT. E. FORSGREN, Klin. Wchnschr. **8**:1110, 1929.

That food intake is the regulating factor of the liver function and of the internal metabolism has been given too much emphasis. Consideration must be given to the fact that the liver has the rhythmic function of alternate assimilation and dissimilation, which to a certain extent is independent of food ingestion. This rhythmic function of the liver certainly is important in carbohydrate metabolism, under normal conditions, as well as in diabetes. The administration of insulin should be correlated not only with food intake, but especially with internal metabolism.

AUTHOR'S SUMMARY.

BEHAVIOR OF CHOLESTEROL ESTERS IN THE SERUM WITH LIVER DISEASE. H. WENDT, Klin. Wchnschr. **8**:1215, 1929.

While the bile of man has a cholesterol ester splitting ferment and therefore contains only cholesterol, the bile of dogs has both cholesterol and cholesterol esters, but no ester splitting ferment. Even the dog's liver has little ester splitting ferment. After ligation of the ductus choledochus in dogs, bile enters the

blood, and there is a parallel increase of cholesterol and cholesterol esters. In man, especially with severe icterus, there is commonly a diminution of the cholesterol esters. This difference in hosts is correlated with the cholesterol ester-splitting ferment of the bile in man.

AUTHOR'S SUMMARY.

THE LACTIC ACID VARIATIONS OF THE BLOOD IN MORBUS BASEDOWI IN REST AND DURING WORK. A. BIER, *Klin. Wchnschr.* 8:1306, 1929.

The lactic acid content of the blood of patients with morbus basedowi during rest is regularly increased. It is either above or at the upper normal limits. With slight effort which in health is scarcely work there is such a marked increase of the lactic acid content that it must debilitate and explain the easily produced fatigue. This increase is proportional to coincident variations in oxygen consumption.

AUTHOR'S SUMMARY.

RELATION OF HEREDITY AND AGE TO OCCURRENCE OF JUVENILE DIABETES MELLITUS. R. PRIESEL and R. WAGNER, *Klin. Wchnschr.* 8:1398, 1929.

The maximum incidence of juvenile diabetes mellitus in the thirteenth year indicates a close relationship between the number of available islets and growth. There is always a congenital deficiency of islets. The manifestation of latent diabetes is dependent primarily on the number of available islets. Juvenile diabetes often is actually not progressive, but only appears to be so. It is hereditary like deformity. Hereditary relations were established in 27 per cent. The greater incidence (43 per cent of their cases) of heredity in diabetes among Jews is due to inbreeding. Diabetes mellitus is inherited as a recessive, as well as a dominant, character.

AUTHORS' SUMMARY.

Pathologic Anatomy

MECONIUM ILEUS WITH CONGENITAL STENOSIS OF THE MAIN PANCREATIC DUCT. BORRIS A. KORNB�ITH and SADAŌ OTANI, *Am. J. Path.* 5:249, 1929.

A case of meconium ileus is presented with the rare anomaly of congenital stenosis of the duct of Wirsung. The absence of pancreatic juice caused inspissation of meconium, with subsequent intestinal obstruction, ileus and perforation.

AUTHORS' SUMMARY.

THE PERCENTAGE OF THE DIFFERENT TYPES OF CELLS IN THE MALE ADULT HUMAN HYPOPHYSIS. A. T. RASMUSSEN, *Am. J. Path.* 5:263, 1929.

The necessity of a more accurate estimation of the relative number of the different types of cells in the anterior lobe of the hypophysis in man is evident from the great divergence of opinion that exists even among recent writers in regard to what should be considered normal proportions, and from the greater attention that is being paid to pathologic conditions of this organ. The results of making a differential count of the chromophobes, acidophils and basophils in the hypophyses of 100 selected and supposedly normal male adults in cases of sudden and accidental death, in which the tissue in general was fixed within twelve hours after death, are presented. The data are based on a differential count of from 10,000 to 30,000 cells from 100 to 350 microscopic fields taken systematically from three different regions of a complete series of horizontal sections from each hypophysis. The chromophobes represent, on an average, 52 per cent of the total cells. They vary from 34 to 66 per cent. The coefficient of variation is 15. The acidophils average 37 per cent, varying from 23 to 59 per cent, the coefficient of variation being 21. The basophils strictly within the anterior lobe are the least numerous and the most variable. The average is 11 per cent, but they range from less than 5 per cent to more than 27 per cent. The coefficient of variation is 34. Fourteen cases showing a body weight of from 200 to 330 pounds (90.7 to 149.7 Kg.) averaged 3.5 per cent

more chromophobes and 4.6 per cent less acidophils when compared with eighty-six cases showing a weight of less than 200 pounds. Statistically this difference is not enough to be taken seriously, although the decrease in acidophils is probably real. There is no correlation of importance between body length and percentage of any particular type of cell. Persons over 50 years of age average nearly 4 per cent more chromophobes and correspondingly less acidophils. There is no correlation between age and basophils in the anterior lobe of the hypophysis.

AUTHOR'S SUMMARY.

A MALIGNANT MEDIASTINAL TERATOMA. WILLIAM F. JACOBS, *Am. J. Path.* 5: 275, 1929.

A case of malignant teratoma is reported. A résumé of the literature indicates that these tumors should be classed as teratomas rather than as dermoids. About 10 per cent of these tumors undergo sarcomatous or carcinomatous transformation.

AUTHOR'S SUMMARY.

TWO OF THE RARER CONGENITAL ANOMALIES OF THE HEART. ISTVAN GÁSPÁR, *Am. J. Path.* 5:285, 1929.

A congenital anomaly of the heart is presented, in which an isolated transposition of ventricles occurred. Both large arteries, the aorta and the pulmonary artery, arose from the left ventricle. This is explained by an imperfect rotation of the septum trunci which divided the truncus arteriosus, causing an aortic stenosis. A very small subaortic defect was found. The independent behavior of the ductus arteriosus and its importance in relationship to the dangerous results of the case are also pointed out.

AUTHOR'S SUMMARY.

MYELOBLASTIC SARCOMA OF THE CRANIUM. EDWIN F. HIRSCH, *Am. J. Path.* 5:303, 1929.

A large myeloblastic sarcoma of the skull with metastases into the right and left deep cervical lymph nodes and into the right lung is described in this report. The tumor and its metastases contained cells that resembled cellular components of the bone-marrow.

AUTHOR'S SUMMARY.

TERATOMA OF THE NECK. O. SAPHIR, *Am. J. Path.* 5:313, 1929.

The literature of teratoma of the neck is reviewed and a new case reported. This is a case of a teratoma of the neck in the region of the thyroid gland in a stillborn colored girl. The main constituent of this tumor was brain tissue but derivatives of the three germinal layers were present. For the first time, groups of cells resembling blood islands are described in this tumor. Even though the location suggests the thyroid gland as the origin, it is more likely that the tumor arose in the area around this gland. The tumor is classified as an embryoid teratoma according to Budde, and as a coetaneous teratoma according to Askanazy.

AUTHOR'S SUMMARY.

THE VESSEL CANALS IN NORMAL AND PATHOLOGICAL BONE. HENRY L. JAFFE, *Am. J. Path.* 5:323, 1929.

Volkman originally reported on the formation of numerous new vessel canals in bone in cases of inflammatory osteoporosis, caries and osteitis, and the presence of a few such canals in normal bone. If the term Volkman canal is used exclusively to designate the structure described by him, then his original conception, that the canals result from the canalization of adult bone by newly formed vessels, is correct. As soon as the term is used to designate such canals as Schwalbe described in ground lamellae, or Axhausen in the middle portion of the compacta, or Schaffer and his co-workers in fetal bone and the bone of the

new-born, one is applying the same name to different structures. In normal bone the canals (other than the haversian canals and the canals of the ground lamellae) which have resulted from the deposition of bone around preformed vessels, and thus are surrounded by lamellae, should be termed communicating vessel canals. These include most of the canals which join the haversian canals. This type predominates. The canals which have resulted from the resorption of formed bone by newly formed vessels, exemplified by those which have ragged borders and no lamellae, are the only canals which correspond with those originally described by Volkmann, and may be called Volkmann's canals. In normal lamellar bone there are very few.

AUTHOR'S SUMMARY.

ELECTRIC SHOCK. H. E. MACMAHON, *Am. J. Path.* 5:333, 1929.

The literature dealing with the pathologic changes in the nervous system of electrocuted animals is reviewed. The observations in normal animals, animals with exposed viscera and animals under atropine which were receiving electric shock are described in detail. The value of repeated sublethal shocks in obtaining histologic lesions is stressed. The rôle of the nervous system in producing changes in other systems is discussed. The gross and microscopic lesions are described in which it is shown that the lesions are confined almost entirely to the nervous system and skeletal muscle. The discussion deals with physical properties of electrical currents, the resistance of the body to currents and the different types of death from electric shock, and emphasis is laid on the importance of prolonged rest in cases of recovery.

AUTHOR'S SUMMARY.

MULTIPLE FOCAL SPLENITIS OF GUINEA-PIGS. WILLIAM H. FELDMAN, *Am. J. Path.* 5:371, 1929.

Twenty-one cases of a spontaneous disease of guinea-pigs which is characterized by a multiple focal type of splenitis, were studied. Morphologically the disease seems to be confined to the spleen, and microscopically the lesions are those of focal necrosis. In an attempt to produce the condition experimentally, thirty-three guinea-pigs were inoculated with emulsions of the lesions from thirteen of the diseased animals. Twenty-five of the experimental animals died; the most frequent lesions were those of purulent or fibrinous peritonitis. From many of the inoculated animals which died, a gram-positive streptococcus was obtained. The spleens of a few of the experimental animals possessed microscopic lesions similar to those observed spontaneously. The impossibility of ruling out spontaneous cases of the disease in the experimental animals makes it unwise to assume that the specific lesions have been produced experimentally. For the same reason there does not seem to be any correlation between the condition known as purulent adenitis and the splenic disease described.

AUTHOR'S SUMMARY.

INVOLVEMENT OF MEDIUM-SIZED ARTERIES ASSOCIATED WITH SYPHILITIC AORTITIS. OTTO SAPHIR, *Am. J. Path.* 5:397, 1929.

Among fifty cases of syphilitic aortitis, the innominate artery showed syphilitic changes in thirty-three, the carotid in twenty-nine, the superior mesenteric in ten, the inferior mesenteric in three, the common iliac in ten, and the femoral artery in seven cases. The subclavian artery was examined in twenty-nine cases, fifteen of which showed syphilitic lesions. The syphilitic lesions were characterized by endarteritis of the vasa vasorum, and perivascular infiltration of lymphocytes in the adventitia. The media of the elastic type of arteries showed an interruption of the continuity of the elastic fibers and fibrotic areas, combined with circumscribed lymphocytic infiltrations. The media of the muscular type of arteries only rarely showed changes. In the intima, circumscribed button-like areas of fibrosis, without degenerative changes, were found frequently. These were not specific but were chronic inflammatory and might be associated with any type of pathologic lesion in the adventitia.

AUTHOR'S SUMMARY.

ACCESSORY PANCREAS. ROBERT A. MOORE, *Am. J. Path.* **5**:407, 1929.

A case of accessory pancreas in the wall of the ileum in a child, aged 1 year, is reported. The mode of origin of these congenital anomalies is either by adhesions of the main pancreatic anlage or from anomalous anlage. Accessory pancreases are in rare instances the underlying cause of diverticula and intussusception and the site of origin of carcinoma.

AUTHOR'S SUMMARY.

LYMPHANGIECTATIC CYST OF THE LEFT LABIUM MINUS. C. J. LUNSFORD and G. C. SCHAUFFLER, *Arch. Dermat. & Syph.* **19**:945, 1929.

A patient with a lymphatic cyst involving the labia minora is added to the five previously reported instances. This account is of interest in that the cyst was limited to the labia minora.

FRANK M. COCHEMS.

GROSS AND MICROSCOPIC CHANGES IN THE SKIN PRODUCED BY X-RAYS AND BY LIPOID SOLVENTS. L. H. JORSTAD and C. W. LANE, *Arch. Dermat. & Syph.* **19**:954, 1929.

Active precancerous lesions histologically were produced in the skin of the white rat by repeated paintings with a diluted tar preparation. The same type of lesion was produced by a single exposure of unfiltered x-rays or by combining the two procedures. In observing the histologic changes produced by these procedures at different intervals throughout the period of experiment, further evidence was gained that coal tar, allied substances such as mazola oil, paraffin oil and foot oil, and roentgen rays act similarly in inducing a malignant condition. They act as lipid solvents.

AUTHORS' SUMMARY.

CHRONIC DERMATOSIS WITH DEGENERATION OF THE COLLAGEN. F. R. HARPER, *Arch. Dermat. & Syph.* **20**:201, 1929.

A case is reported of a chronic, noninflammatory, widespread, symptomless disease of the skin. In the sections of tissue obtained by biopsy there was swelling and degeneration of the collagen bundles of the subpapillary layer of the corium, with an associated decrease in the size and number of the elastic fibers and an increase in the nuclear elements. The author concludes that the disease is probably a combined degeneration and proliferation involving the subpapillary layer of the corium.

AUTHOR'S SUMMARY.

GENERALIZED LYMPHOGRANULOMATOSIS OF THE SKIN. J. W. JONES and H. S. ALDEN, *Arch. Dermat. & Syph.* **20**:212, 1929.

An instance of generalized lymphogranulomatosis in a negro boy is reported. The noteworthy features were a generalized intense pruritic eruption, a hyperplasia of the lymph nodes and an ultimate loss of hair. These symptoms give the disease a certain clinical similarity to pityriasis rubra (Hebra). In the histologic preparations of a lymph node from the right inguinal region there were no giant cells.

FRANK M. COCHEMS.

NEPHROSIS (A CRITIQUE). HENRY A. CHRISTIAN, *J. A. M. A.* **93**:23, 1929.

The following conception is advanced of nephrosis as a clinical condition: With a prolonged protein deficit in the blood there will appear edema, lowered blood protein with relative increase of globulin, hypercholesteremia and lowered basal metabolism. The most common cause of deficit in blood protein is albuminuria due to a renal lesion. Often this renal lesion is in the glomeruli, but in patients dying of infection rather early, the glomeruli may be but little altered or not at all, while there are extensive changes of a degenerative nature in the tubules. There

seems "to be no justification for regarding nephrosis as other than a variety of kidney disease, a form of chronic nephritis (Bright's disease)." Clinically nephrosis does not mean that a deposit and single form of lesion is present in the kidney, as there may be degeneration of tubules with normal glomeruli, amyloidosis, or glomerular lesions; furthermore all these changes may occur in patients without any syndrome of nephrosis. Nephrosis as a clinical term has no advantage over such terms as subacute or chronic nephritis with edema. The use by pathologists of the term nephrosis for degenerative renal lesions may not be objectionable, but clinicians will still be unable to apply a pathologic (anatomic) classification of nephritis accurately in clinical work.

ASCARIS LUMBRICOIDES IN CAVITY OF HEART. CARL BOETTIGER and JACOB WERNE, J. A. M. A. **93**:32, 1929.

Two worms were found in the cavity of the right ventricle in a woman, aged 65.

ISLET CELL TUMOR OF THE PANCREAS, GOLDWIN HOWLAND and others, J. A. M. A. **93**:674, 1929.

In a case of dysinsulinism of six years' duration, attacks of coma and convulsions increasing in their frequency but warded off by the administration of food were found to be caused by low blood sugar levels. A study of the case revealed the erratic response to carbohydrate administration unless suitably administered, and led to the diagnosis of the cause as an islet cell tumor of the pancreas. At operation a tumor of the pancreas was found and removed, and a fruitless search for metastases was made. The patient recovered and has since been entirely free from the attacks. This constitutes the first successful treatment in such a case reported in the literature. The tumor was found to be a slow growing carcinoma of the islets of Langerhans, and insulin was recovered from the tumor mass.

AUTHORS' SUMMARY.

MEASUREMENTS OF THE PELVIS IN HINDU FEMALES. N. PAN, J. Anat. **63**:263, 1929.

Measurements were taken from the pelves of sixty-four adult Hindu women. The author found that the pelvis of women of this race is 1 cm. less in all diameters than that of British or American women. The fact that the body of the fetus is comparatively smaller in size prevents obstetric difficulties.

A. J. KOBAR.

THE ETIOLOGY OF ACCIDENTAL HEMORRHAGE AND PLACENTAL INFARCTION. F. J. BROWNE and GLADYS DODDS, J. Obst. & Gynaec. Brit. Emp. **35**:661, 1928.

Browne and Dodds reproduced accidental hemorrhage (premature separation of a normally implanted placenta) experimentally in rabbits by first inducing a chronic nephritis in the nonpregnant animal, and caused an exacerbation of the renal lesion after twenty days of pregnancy (corresponding to six months pregnancy in the human being). Sodium oxalate 1 per cent was given at frequent intervals intravenously for three months; after twenty days of pregnancy this was given once more, followed by an injection of an emulsion of *Bacillus pyocyaneus*. This was repeated on several rabbits and the results were constant. The hemorrhage was retroplacental, intramuscular and at times visible as a bleeding through the vagina. The authors offer a newer concept as to the pathogenesis of the associated infarction in the placenta. They express their belief that the same process which evokes the toxemia of pregnancy causes the infarction, namely, a circulating endothelial toxin. The latter destroys the syncytial living of the villus, permitting a clot to form around it and cut off its source of nutrition. This endothelial poison acts likewise on the endothelium of the decidual

capillaries and on that of the vessels in the fibromuscular wall of the uterus and its adnexa. Changes were similarly noted in distant organs, such as the brain, liver and spleen. These experiments were well controlled, and examinations of the urine and blood chemistry were used as checks. Subsequent pregnancies in animals that survived these experiments were associated with spontaneous premature detachment of normally implanted placentae. From their experimental data the authors conclude that chronic nephritis is the essential underlying factor; when it is present, the kidneys cannot normally eliminate the circulating toxins (metabolic or bacterial) but allow them to accumulate and concentrate, and cause capillary endothelium destruction with thromboses and hemorrhages.

A. J. KOBAK.

A CASE OF ADENOMYOLIPOMA OF THE FALLOPIAN TUBE. WILFRED SHAW, J. Obst. & Gynaec. Brit. Emp. **35**:725, 1928.

Shaw describes a rare tumor occurring in a nullipara, aged 40, whose chief complaint was irregular hemorrhage. Laparotomy disclosed that there was a left tubo-ovarian cyst, that the right tube and ovary were covered with adhesions, and that the uterus contained fibroids. The right cornu appeared to contain a small lobulated fibroid, which when incised allowed some tarry fluid to escape. The tumor arose from the anterior surface of the isthmic portion of the fallopian tube. Histologically, the glandular tissue in serial sections appeared to be connected with the mucosa but was entirely separated from other glandular spaces that were seen deeper in the muscular planes. These gland spaces were lined partly by cuboidal cells, and no peripheral stroma was present. As there was no connection with the serosal and mucosal surfaces of the uterus, Shaw believes that these deep gland spaces arose by a metaplasia of the endothelial lining of the lymphatic spaces. There were also some muscle and gland spaces among the fat cells of the lipoma. The author does not believe there is any reason for associating the adenomyoma with the chronic inflammatory condition of the tube.

A. J. KOBAK.

INSERTION OF PAPILLARY MUSCLES DIRECTLY INTO THE FRONT MITRAL LEAFLET. H. WILLER, Centralbl. f. allg. Path. u. path. Anat. **45**:209, 1929.

Willer describes two hearts in which there was a direct attachment of portions of the left anterior papillary muscle to the front mitral leaflet. The first he observed in a man, aged 63, who was dying of hemorrhage following rupture of the spleen; the second in a woman, aged 26, who was dying of peritonitis. The site of attachment was 6.5 mm. long and 4 mm. wide in the first case, and 10 mm. long and 4 mm. wide in the second. Short chordae tendineae were stretched from the edges of these muscle bands to the mitral leaflets. In both cases there were separate portions of the muscle, some inserting directly and some connecting by chordae. Presumably these muscles are congenital anomalies which may be accentuated by hypertrophy in such a disease as mitral insufficiency.

GEORGE RUKSTINAT.

PROGRESSIVE THROMBOPHLEBITIS. M. LIPSCHITZ, Deutsche med. Wchnschr. **55**:744, 1929.

A man, aged 49, with no essential previous history suffered a contusion of the right leg. The resultant swelling of the leg increased and the veins beneath the skin became firm, tender cords. Four months later the left lower leg became swollen and discolored, and the subcutaneous veins also firm and tender. Finally there was thrombosis of the veins of the lower anterior abdominal wall and of the right internal jugular vein. This was followed by ocular paralysis and a left hemiplegia.

Postmortem examination demonstrated thrombosis of the small veins of both legs, of the anterior abdominal wall and of the prostatic plexus. There were mural thrombi of both common iliac veins and inferior vena cava to the level of the renal veins. The lumen of the right saphenous and femoral veins contained canalized thrombi. An organizing thrombus of the right internal jugular vein extended into the dural sinuses and caused hemorrhagic infarcts of the brain. There was a marked senile arteriosclerosis of the aorta with occlusion of the left coronary artery and an aneurysm of the heart. The spleen was enlarged. The leukocytes of the blood were unchanged and the Wassermann reaction of the blood was negative. Blood cultures were also negative.

PAUL J. BRESLICH.

UNUSUAL AMYLOID DEPOSITS. O. LUBARSCH, *Virchows Arch. f. path. Anat.* **271**:867, 1929.

In very rare instances, general amyloidosis attacks the organs that generally remain free, and leaves intact or nearly intact the large parenchymatous organs that are usually involved. Lubarsch describes three such cases in detail. In one of them the amyloidosis of the muscle system and the skin had led to a clinical diagnosis of scleroderma and myotony, while the involvement of the tongue gave a picture of carcinoma. The walls of the heart had become so stiff from the amyloid deposits that the heart retained its form after being opened. In the skin the amyloid formed circumscribed nodules. In other respects, too, this condition was intermediate between generalized amyloidosis and localized amyloid deposits. The blood vessels appeared gaping at autopsy due to the stiffness of their walls. The media was mostly affected. The nervous system was practically free. In a second case the involvement of the lymph nodes, together with gastric ulcers, had resulted in a picture of inoperable cancer of the stomach. The third patient showed purpura and diseased gums in spite of good nourishment.

The color reactions were partly anomalous. In the first case no underlying disease could be found. The inflammatory processes (pyelitis urethritis) that could be traced in the two other ones seem unimportant in comparison with the enormous amyloidosis. But, as animal experiments indicate, amyloidosis may become progressive even after cessation of the causative disease.

ALFRED PLAUT.

THE PHYSIOLOGY AND HISTOLOGY OF THE MUMMIFIED RABBIT'S EAR. B. D. MOROSOW, *Virchows Arch. f. path. Anat.* **272**:1, 1929.

Organs dried in the exsiccator, even for months, and then softened in water may retain some of their functions. This has been shown in the ear of the rabbit, the fingers of the human being, the intestine of the rabbit and the guinea-pig and the heart of the frog.

Morosow worked on forty dried rabbit's ears. The drying was done in different ways: in the exsiccator, in thin air, at room temperature and in hot air. It was continued until the weight became constant (in from fifteen to 119 days). The loss of weight was from 54 to 73 per cent; the dried ear looked like parchment, but not all the water had left the tissue. The blood vessels of these dried ears reacted to epinephrine (from 0.25 to 1.0 cc.), nicotine 1:200, cocaine 1:200, and barium chloride 1:200. No reaction could be obtained with caffeine, caffeine sodium benzoate, chloral hydrate or the faradic current. These dried tissues can be stained as well as normal tissues can.

ALFRED PLAUT.

MARKINGS OF THE CUT SURFACE OF LIVER. L. LOEFFLER, *Virchows Arch. f. path. Anat.* **272**:17, 1929.

Acinar markings of the cut surface are pathologic. The really normal liver—which is seldom seen at autopsy—has a nearly homogeneous cut surface. Overgrowth of the interlobular connective tissue leads to a tortuous course of the interlobular veins. These are cut frequently and more or less longitudinally,

hence the red bands of the nutmeg liver. Large livers with small acini are found in hypertension when death has taken place without long illness. Such livers have much parenchyma, little connective tissue but much muscle tissue in the vessel walls. Lobar structure is found in heart disease, mitral stenosis, and cirrhosis—Laennec's as well as the syphilitic type. Overgrowth of connective tissue may take place along the different blood vessels of the liver, and anastomoses may be established in different ways; this leads to different aspects of the cut surfaces. All the manifold pictures are caused by the reactions of the vascular apparatus of the liver. Direct damage to the liver cells plays no rôle.

ALFRED PLAUT.

THE INTERVERTEBRAL DISKS. E. BRACK, *Virchows Arch. f. path. Anat.* **272**:61, 1929.

One fifth to one sixth of the length of the spine belongs to the disks. Too little is known about their normal structure. They are nourished by osmotic exchange mainly, but there are blood vessels at the periphery. The upper and the lower layers consist of cartilage; these layers are thicker in children, and very thick in rickets. There is much variation in the normal shape of the disks. Traumatic tearing occurs even without bone lesion. In some instances of bone atrophy the disks dig a funnel into the middle of the vertebrae. Circumscribed hypertrophy is frequent in the form of Schmorl's "Knorpelknötchen" (cartilaginous nodules). They usually have the shape of a button. They seem single, occasionally double, to the naked eye; on microscopic examination they often are multiple. They are more frequent in men than in women; the thoracic spine harbors them most frequently. Small foci of nucleus pulposus tissue situated in the annulus fibrosus may have something to do with their origin. Their cells store fat, while the normal cells of the nucleus do not. Small margins of bone marrow may become necrotic when touched by a cartilaginous nodule. The edge of the nodule slowly calcifies.

In twelve cases of most severe traumatism, hemorrhage was not found in the disks. In old people, however, brownish discoloration is found occasionally. Atrophy occurs in kyphoscoliosis and in old age. The disks become narrow, and the annulus may become cartilaginous, notably in arthritis deformans. The disks offer a new but difficult field for study. The present study is based on 100 spines.

ALFRED PLAUT.

THE PATHOLOGIC ANATOMY OF LYMPHOGRANULOMATOSIS. M. BRANDT, *Virchows Arch. f. path. Anat.* **272**:401, 1929.

Sixty-five cases were observed in Riga (Latvia) from 1922 to 1928. Mesenteric and retroperitoneal lymph nodes were often affected. The classic textbook picture with main localization on the neck was rare. The spleen was nearly always affected. The eosinophil cells in the tissue are not important for diagnosis. Varying forms of giant cells were found besides the Sternberg cells; some of them resembled the Langhans cell and were phagocytic. The lymphogranulomatous tissue changes indicate a severe damage to the reticulo-endothelium. The causes of such damage are not uniform. Lymphogranulomatosis is no disease in itself.

ALFRED PLAUT.

Pathologic Chemistry and Physics

THE EXCRETION OF LEAD IN URINE. H. MILLET, *J. Biol. Chem.* **83**:265, 1929.

Lead is a normal constituent of the urine. The daily excretion of the metal by persons who have received injections of colloidal lead phosphate does not appear to exceed that observed in persons not so treated.

ARTHUR LOCKE.

BIOCHEMICAL FINDINGS IN A RARE CASE OF ACUTE YELLOW ATROPHY OF THE LIVER, WITH PARTICULAR REFERENCE TO THE ORIGIN OF UREA IN THE BODY. I. M. RABINOWITCH, *J. Biol. Chem.* **83**:333, 1929.

A case of idiopathic, acute yellow atrophy of the liver is described. The patient had, functionally, the status of a person from whom the liver and kidneys had been completely removed. No urea was present in the blood and extremely little in the urine, suggesting that the substance may be formed only through the agency of intact liver tissue.

ARTHUR LOCKE.

THE HYDROGEN-ION CONCENTRATION OF SWEAT. A. MARCHIONINI, *Klin. Wchnschr.* **8**:924, 1929.

The p_H of sweat secretion obtained by thermal (light) stimulation and injection of pilocarpine, collected separately from the apocrine and the eccrine glands, differs considerably. The p_H of sweat from the eccrine glands varied between 4.0 and 5.5, that from the apocrine glands between 6.0 and 6.9 with thermal stimulation. With pilocarpine stimulation, the corresponding p_H values were from 5.1 to 7.3 and from 7.2 to 8.6, again showing distinct differences.

EDWIN F. HIRSCH.

EXPERIMENTAL ALKALOSIS AND THE GASEOUS EXCHANGE IN MAN. O. WUTH, *Klin. Wchnschr.* **8**:969, 1929.

Fifty grams NaHCO_3 given by mouth to an obese but robust young man (17 years old) cause a marked alkalosis and an increase of the basal metabolism from -3 to $+14$.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

FULMINATING MENINGOCOCCUS SEPTICEMIA WITHOUT MENINGITIS. RICHARD MIDDLETON and WILLIAM DUANE, *Am. J. M. Sc.* **177**:648, 1929.

A case is presented in which a fulminating infection with meningococcus caused death within a few hours, the only clinical and anatomic observations being those of an intense septicemia.

PEARL ZEEK.

INFECTION AS A CAUSE OF JUVENILE CIRRHOSIS. V. H. MOON, *Am. J. M. Sc.* **177**:681, 1929.

Juvenile cirrhosis is a combined disease of liver and spleen. Streptococci were found in these organs in two cases of atrophic cirrhosis in children. The streptococci from one case showed a definite tendency to infect the liver in animals, regardless of the route or site of inoculation.

PEARL ZEEK.

RETROPHARYNGEAL ABSCESS IN INFANTS AND CHILDREN. HARRY M. GREENWALD and CHARLES A. MESSELOFF, *Am. J. M. Sc.* **177**:767, 1929.

The importance of this condition is emphasized in the analysis of fifty-five cases among which the death rate was 7.3 per cent. Retropharyngeal abscess should be suspected in every case presenting an enlarged cervical gland and the diagnosis determined by digital examination of the pharynx.

PEARL ZEEK.

GONOCOCCAL AND PNEUMOCOCCAL VEGETATIVE ENDOCARDITIS OF THE PULMONARY VALVE. JAMES I. JOHNSTON and JOHN M. JOHNSTON, *Am. J. M. Sc.* **177**:843, 1929.

Two cases of acute lesions of the pulmonary valve are described in which the etiologic agents were presumptively found.

PEARL ZEEK.

THE BLOOD SEDIMENTATION TEST IN EXPERIMENTAL POLIOMYELITIS. J. R. KAGAN, *Am. J. M. Sc.* **178:67**, 1929.

The sedimentation time for normal healthy monkeys was determined and found to be nineteen hours and thirty-two minutes. The sedimentation time for monkeys with poliomyelitis is considerably shorter, giving an average of two hours and thirty-nine minutes, and showing a marked difference from the sedimentation time for normal monkeys. The sedimentation time for monkeys with tuberculosis, general debility of undetermined nature and superficial infection is still shorter, namely, one hour and twenty minutes.

AUTHOR'S SUMMARY.

STRAIN VARIATIONS IN *C. BIFERMENTANS*. E. T. DRAKE and W. S. STURGES, *J. Bact.* **17:387**, 1929.

With the assumption that *Clostridium bifermentans* and *C. centrosporogenes* constituted a somewhat unified group, a study was made of all available strains (twenty-one) belonging to this group. Since no consistent differences were found between the strains labeled *C. bifermentans* and those labeled *C. centrosporogenes*, the use of the latter name would seem unjustifiable. The variations observed suggest another and a more logical grouping, but the nature of the variations and the existence of intermediate strains necessitate all of the strains being considered as a single species.

AUTHORS' SUMMARY.

THE INFLUENCE OF IRON ON THE PIGMENTATION OF ACID-FAST BACTERIA. GUILFORD B. REED and CHRISTINE E. RICE, *J. Bact.* **17:407**, 1929.

Data have been presented which indicate that the yellow, brown or red pigmentation of acid-fast bacteria is related to the presence of iron in the culture mediums. Lack of stabilizing substances or high p_H which permits precipitation of the iron prevents pigment formation. Nonacid-fast bacteria are not so affected by the iron content of culture mediums.

AUTHORS' SUMMARY.

CLASSIFICATION OF THE STREPTOCOCCI OF HUMAN FECES. HENRY WELCH, *J. Bact.* **17:413**, 1929.

The streptococci of the feces are apparently constant in their fermentative ability. Differentiations should be made only in mediums which are most favorable for the growth of the organism. The results indicate that there are six strains common to stools of human beings. Those fermenting all sugars used, dextrose, lactose, sucrose, salicin, maltose, mannitol, galactose; all but sucrose; all but sucrose and mannitol; all but mannitol; all but mannitol and saicin; all but actose. Serologically, strains *a*, *c* and *d* resemble each other and give slight hemolysis. Strains *b*, *e* and *f* give no hemolysis, and of these *b* and *f* resemble each other serologically, while *e* is distinctly different. There is little in the morphology of the streptococci of the feces of human beings that assists in their differentiation.

AUTHOR'S SUMMARY.

THE GERMICIDAL ACTION OF HALOGEN DERIVATIVES OF PHENOL AND RESORCINOL AND ITS IMPAIRMENT BY ORGANIC MATTER. EMIL KLARMANN, VLADIMIR A. SHTERNOV and JOHN VON WOWER, *J. Bact.* **17:423**, 1929.

The results of experiments on the disinfectant action of phenol, resorcinol and their halogen derivatives, against *B. typhosus* and *Staphylococcus pyogenes-aureus*, tend to indicate that there is a distinct relationship between the constitution of these derivatives and the impairment of their disinfectant action by organic matter. It is shown that even the exceedingly small quantity of organic matter present in the original culture suffices to produce considerable impairment of the germicidal efficacy of certain compounds. A working hypothesis of disinfectant action is outlined, depending on the assumption of formation of so-called molecular (additive)

compounds of the disinfectant agent with certain free reactive groups in the organic matter, or the protoplasm, respectively, which is to form the basis for further work on the problem.

AUTHORS' SUMMARY.

THE INFLUENCE OF GASEOUS ENVIRONMENT ON GROWTH AND TOXIN PRODUCTION OF *C. DIPHTHERIAE*. WAYNE N. PLASTRIDGE and LEO F. RETTGER, J. Bact. **18**:1, 1929.

The intracutaneous test, as employed in this investigation, was found to be a reliable and economical means of determining the approximate toxicity of *C. diphtheriae* culture filtrates. Aeration of broth cultures of *C. diphtheriae* with atmospheres containing from 3 to 10 per cent carbon dioxide and from 5 to 50 per cent oxygen resulted in increased growth and toxin production. Aeration of broth cultures with ordinary air or carbon dioxide-free atmospheres containing from 10 to 50 per cent oxygen resulted in marked irregularity in growth and in the toxin content of *C. diphtheriae* cultures. The data obtained show that the higher the oxygen content of the atmospheres passed over the cultures the greater is the irregularity in toxin content of the cultures at the time of harvesting. The rate of destruction of the toxin once it was formed was found to be inversely proportional to the oxygen tension within the culture flask. The optimum oxygen and carbon dioxide tensions for growth and toxin accumulation were found to be supplied by an atmosphere containing from 15 to 20 per cent oxygen and from 5 to 10 per cent carbon dioxide. In the presence of such an atmosphere uniform maximum toxin production occurred in a given medium, and no decrease in toxicity took place on prolonged incubation. The reaction of cultures of *C. diphtheriae* which were grown in meat-infusion broth prepared with Difco-Proteose Peptone was maintained at about p_H 8, 7.8 and 7.5 by aeration with atmospheres containing 5, 10 and 20 per cent carbon dioxide, respectively. The ammonia content of all cultures showed a sharp increase during the period of maximum growth. In the case of the cultures grown under ordinary atmospheric conditions, or aerated with carbon dioxide-free atmosphere, this increase was followed by a gradual decline, as compared to a continuous increase throughout the entire twenty-day incubation period in cultures grown under an increased carbon dioxide tension. The amino-nitrogen increase in cultures grown in broth prepared with Difco-Bacto Peptone, was much less marked than in cultures grown in broth prepared with Difco-Bacto Peptone, presumably due to a dearth of protein derivatives in Difco-Bacto Peptone which are capable of being broken down into amino-acids by the peptolytic enzymes of *C. diphtheriae*. The proteose fractions of certain commercial peptones were found to be necessary for toxin formation for other reasons than their buffering action on decreasing hydrogen ion concentration of the culture medium. Increased carbon dioxide tension was found to prevent the usual rapid destruction of the bacterial cells after the period of maximum growth. The general conclusion may be drawn from the data presented that carbon dioxide plays an important rôle in the growth and toxin production of *C. diphtheriae*, mainly by: acting as either a catalyst or food in stimulating growth and toxin formation; controlling the reaction of the culture medium during growth and preventing the destruction of the toxin once it is formed, by a mechanism which is as yet little or not at all understood.

AUTHORS' SUMMARY.

SODIUM CHLORIDE MEDIA FOR THE SEPARATION OF CERTAIN GRAM-POSITIVE COCCI FROM GRAM-NEGATIVE BACILLI. JUSTINA H. HILL and EDWIN C. WHITE, J. Bact. **18**:43, 1929.

It has been found that p_H 6 sodium chloride agars, with salt concentrations from 2 through 20 per cent, exert marked inhibitory action on the growth of bacilli of the typhoid, paratyphoid, dysentery, and colon groups, on species of *Proteus*, *Pseudomonas*, on diphtheroids and on *Bacillus anthracis*. The gram-positive cocci studied tolerate high salt concentrations, all being positive on transfer from 20 per cent sodium chloride agar. In p_H 6 broths, with salt concentrations

from 2 through 25 per cent, the same differential bacteriostasis may be observed, although to a lesser degree than on agar. It has been found that when mixtures of cocci and bacilli in different proportions are cultured on appropriate salt agars, the cocci invariably outgrow the bacilli and may sometimes be recovered in pure culture. The use of 6, 8, 10 and 15 per cent salt agars greatly facilitates the isolation of gram-positive cocci from specimens from mixed infections. The use of such salt agars is therefore suggested for the inhibition of gram-negative bacilli and for the isolation of gram-positive cocci.

AUTHORS' SUMMARY.

A CONTINUOUS METHOD OF CULTURING BACTERIA FOR CHEMICAL STUDY. HARVEY V. MOYER, J. Bact. **18**:59, 1929.

A continuous process for culturing bacteria in the laboratory for chemical study has been described. The construction and operation of the apparatus have been discussed. The mass production of *Bacterium aerogenes* has been described.

AUTHOR'S SUMMARY.

AN OUTBREAK OF BOTULISM DUE TO HOME-CANNED STRING BEANS. WILLIAM E. CARY, STEWART A. KOSER and VAN S. LAUGHLIN, J. Prev. Med. **3**:317, 1929.

An outbreak of botulism at Westfield, N. Y., resulting in ten cases with five deaths, was evidently due to home-canned yellow string beans. *Clostridium botulinum*, type B, was isolated from the empty jar which had contained the beans. Another product from the same household, home-canned egg plant, was found to be lightly seeded with *Clostridium botulinum*, type B, though the food itself was nontoxic.

AUTHORS' SUMMARY.

THE IDENTITY OF HUMAN LEPROSY AND RAT LEPROSY. ERNEST L. WALKER and MARION A. SWEENEY, J. Prev. Med. **3**:325, 1929.

The morphologic and tinctorial transmutations of the organism of rat leprosy are identical with those of the human strains. The authors are convinced that leprosy in the rat and in the human being has the same etiology and endemology, i. e., is caused by an actinomyces infection from the soil. The discovery of this identity is of especial importance because it provides an experimental animal for the study of the disease.

FACTORS INVOLVED IN AN EFFECTIVE TYPHOID CARRIER SURVEY. LEON C. HAVENS and CATHERINE RIDGWAY, J. Prev. Med. **3**:335, 1929.

A typhoid carrier survey of 225 food handlers in a small Southern city revealed seven carriers (three typhoid and four paratyphoid B). The importance of well organized and carefully planned field work is emphasized as an essential part of a carrier study of any extent. Carrier surveys, particularly of food occupations, yield results, in the Southern States at least, which justify their inclusion among typhoid control measures.

AUTHORS' SUMMARY.

SEASONAL VARIATION IN THE SUSCEPTIBILITY OF MICE TO DYSENTERY (SHIGA) TOXIN. ADELAIDE V. BLAKE and C. C. OKELL, Brit. J. Exper. Path. **10**:175, 1929.

In titrations of dysentery (Shiga) toxin and antitoxin, not only are variations in individual susceptibility to the toxin met with, but also variation effects in groups of mice used at intervals. The variability appears to be seasonal, the mean susceptibility of the mice to the toxin being greater in winter than in the summer months.

The possibility of variations of this type must be considered in titrations of any biologic reagent where the degree of accuracy demanded approaches nearly to the extreme limits permitted by the method of test.

AUTHORS' SUMMARY.

THE NATURE OF TUBERCULOUS CASEATION. W. PAGEL, Klin. Wchnschr. 8:1352, 1929.

In an experiment in which human tuberculous tissues were transplanted into skin pockets of normal and tuberculous guinea-pigs, two varieties of tuberculous softening could be distinguished: (1) circumscribed softening in nonallergic animals in close relation with local bacterial proliferation; and (2) extensive leukocyte digestion of the transplanted tissues in allergic animals.

AUTHOR'S SUMMARY (in part).

ON LYMPHOGRANULOMATOSIS AND OTHER PECULIAR GENERALIZED GRANULOMAS OF LYMPH NODES. K. TERPLAN and MARIA MITTELBACH, Virchows Arch. f. path. Anat. 271:759, 1929.

The authors report observations on twenty-nine cases of lymphogranulomatosis in which complete examinations were made. The total number that came to autopsy in four years was thirty-five. The authors do not believe that lymphogranulomatosis has anything to do with tuberculosis. The histologic pictures of tuberculosis and lymphogranulomatosis when coexistent could be differentiated easily from each other. Animal inoculations were positive in three cases only; in one there was active tuberculosis, and there was an old tuberculous condition in the two other cases. Lymphogranulomatosis is a chronic, specific, infectious disease. The combination with tuberculosis was found in one sixth of the cases. An attempt was made to correlate the main seat of the disease with the localization of the first clinical symptoms; but a definite relation was apparent in the intestinal cases only. It is astonishing that of twenty-nine cases seven were intestinal. On the other hand the spleen, which by some authors is considered to be always affected, was found free in one third of the cases. The fibrosis is not present in all cases of long duration. There seems to be a relation between age and duration, the chronic forms being more frequent in young patients, acute ones (with less than six months' duration) in older people. The biopsy diagnosis could not be made in seven cases. Moderate leukocytosis with lymphopenia is the rule. Eosinophilia plays no rôle. Four of the cases are doubtful and may be inflammatory hyperplastic processes of specific nature different from lymphogranulomatosis. Two cases are early; one of them represents an accidental finding of lymphogranulomatosis of the nodes in a man who died of pneumonia. Atypical forms should be studied carefully and collected, but one should not give new names to them. Lymphogranulomatosis is much more frequent than any systemic disease of the lymphatic apparatus. There was one localized blastoma-like granuloma of the intestine. Only fifteen or sixteen cases of the twenty-nine were typical, and they too partly looked uncharacteristic and gave a variety of histologic pictures. In three instances blastoma-like pictures were found in addition to a typical lymphogranulomatosis. Lymphocytic hyperplasia is not a feature of typical lymphogranulomatosis. Overgrowth of reticulum cells is found in early stages. Plasma cells perhaps develop out of reticulum cells too. For the many details of the paper the reader must be referred to the original.

ALFRED PLAUT.

Immunology

BRUCELLA ABORTUS IN MILK SUPPLY AS A SOURCE OF AGGLUTININS IN HUMAN SERA. MERRILL J. KING and DOROTHY W. CALDWELL, Am. J. M. Sc. 178:115, 1929.

Persons with lowered resistance who drink raw milk infected with *Brucella abortus* may develop agglutinins in their blood serum with or without the manifestation of appreciable clinical symptoms of undulant fever. Of 851 patients and 156 staff members in a sanatorium in which raw milk was used, 91, or 9 per cent, showed abortus agglutinins when their serums were diluted 1:15 or higher. Twenty-four of the ninety-one had agglutinin titers varying from 1 to 45 to 1 to

3,200. The presence of abortus agglutinins in human serum is evidence of infection with *Brucella abortus*. The agglutinins may persist in the serum for months or years after the recovery of the patient. There is complete lack of evidence of porcine infection in our herd. The correlation between the periods of *Brucella abortus* infection of the milk supply and the occurrence of agglutinins in the serums of the patients indicates a bovine origin of the cases of undulant fever reported in this study. *Brucella abortus* may be present in small numbers in the milk of infected cows, but the organisms may be eliminated for several years. The presence of *Brucella abortus* agglutinins in the blood serums of cows does not determine whether they are discharging *Brucella abortus* in their milk. In a herd of 151 animals, no evidence was obtained of the infection of the milk of cows whose serums agglutinate at 1 to 60, while cultures of *Brucella abortus* were obtained from the milk of only 23 of 56 cows with titers of 1 to 120 or higher. *Brucella abortus* was not isolated from the blood or from the urine of the infected cows.

AUTHORS' SUMMARY.

ALLERGIC PURPURA. H. L. ALEXANDER and C. H. EYERMANN, J. A. M. A. **92**: 2092, 1929.

Cases are described of purpura with abdominal pain following the ingestion of particular foods.

COTTONSEED AND KAPOK SENSITIZATION. G. T. BROWN, J. A. M. A. **93**:370, 1929.

Cottonseed and kapok ("silk floss") may give rise to apparently specific sensitization in the form of asthma and other allergic reactions. The cotton plant and the kapok tree are related. It is recommended that patients with nonseasonal allergy be tested with cottonseed protein.

SKIN HYPERSENSITIVENESS OF PATIENTS WITH RHEUMATIC FEVER AND CHRONIC ARTHRITIDES TO FILTRATES, AUTOLYSATES AND BACTERIAL SUSPENSIONS OF STREPTOCOCCI. KONRAD E. BIRKHAUG, J. Infect. Dis. **44**: 363, 1929.

A series of 3,114 skin tests was performed during the summer of 1928 in European clinics on 594 persons among whom were 42 active and 146 inactive or "cured" cases of rheumatic fever, carditis and chorea, 69 cases of chronic infectious and degenerative arthritides and 337 nonrheumatic controls.

An excessive universal hypersensitiveness (allergy) was found among 68 per cent of all types of acute rheumatic fever infection to the filtrates, autolysates and bacterial suspensions produced by the indifferent nonmethemoglobin-forming streptococcus and *S. viridans*; while only 22 per cent reacted to the filtrates and 36 per cent to the autolysates and bacterial suspensions produced by the hemolytic streptococcus.

Hypersensitiveness to nonhemolytic streptococcal products is most marked among active cases of rheumatic infection (72 per cent); these cases react almost equally well with filtrates boiled for four hours (67 per cent), while 64 per cent of inactive cases react to nonhemolytic streptococcal products and 25 per cent to the boiled filtrates. Only 33 per cent of patients with active and 29 per cent of those with inactive rheumatic fever react to hemolytic streptococcal products, while 25 per cent of the nonrheumatic controls react to the hemolytic and 14 per cent to the nonhemolytic streptococcal products.

Among a series of 69 cases of chronic arthritides, 53 cases were due to infectious processes, and 47 per cent of these reacted markedly to the products of both nonhemolytic and hemolytic streptococci.

It appears that a nonspecific, common allergenic factor is present excessively in the bacterial products of indifferent and viridans streptococci and moderately

present in solutions of hemolytic streptococci, to which patients with either acute rheumatic infections or chronic infectious arthritides react hyperergically.

AUTHOR'S SUMMARY.

SKIN REACTIONS TO FILTRATES AND KILLED CULTURES OF GREEN-PRODUCING COCCI IN RELATION TO MEASLES. WILLIAM L. BRADFORD, J. Infect. Dis. **44**:378, 1929.

No definite relationship was found to exist between the immune and non-immune to measles as determined by cutaneous reactions to the toxic filtrates and antigens of certain green-producing cocci, including the Tunncliff coccus, the organism of Duval and Hibbard and *Streptococcus morbilli* of Ferry.

AUTHOR'S SUMMARY.

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI. JAMES M. NEILL AND WILLIAM F. FLEMING, J. Infect. Dis. **44**:397, 1929.

The hypersensitiveness described agreed with the previous example of diphtheria hypersensitiveness in two respects: there were immediate skin reactions to either diphtheria or xerosis diphtheroid material, and the hypersensitive reactivity could be transferred to local skin areas of normal persons. The two states of hypersensitiveness were not identical however. The first distinction was that the ratio of diphtheria reactivity to xerosis reactivity was different for the two persons; the one being more reactive with the xerosis diphtheroid than with diphtheria, the other being more reactive to diphtheria than to the diphtheroid. The second distinction was that the one was reactive with a heat stable constituent of the diphtheroid filtrate while the diphtheroid constituent to which the other person reacted was heat labile. Although both persons gave the same type of skin reaction to both the diphtheria and the diphtheroid bacteria, the described distinctions suggest a difference in the bacterial origin of their sensitization.

AUTHORS' SUMMARY.

PASTEURELLA PESTIS DETOXIFIED WITH FORMALDEHYDE FOR IMMUNIZATION AND AGGLUTINATION TESTS. A. BATCHELDER, J. Infect. Dis. **44**:403, 1929.

Pasteurella pestis antigens prepared with 0.85 per cent sodium chloride solution containing a diluted solution of formaldehyde U. S. P. (1:25) are killed within seven to eight hours. The suspensions are smooth and stable. Immunization of laboratory animals for the production of agglutinating serums may be readily accomplished by giving a small number of large intravenous doses of such antigens in rapid succession. The serums so produced are of moderately high titer, but highly specific. The agglutination reaction with suspensions and serums produced in this manner is of the readily visible, flocculent type.

AUTHOR'S SUMMARY.

ISOHEMOLYSINS. CORNELIA M. DOWNS, H. P. JONES and KENNETH KOERBER, J. Infect. Dis. **44**:412, 1929.

Isohemolysins were present in 65.9 per cent of the serums from white persons and in 49.5 per cent of the serums from Indians. The failure of hemolysin in the fresh serums tested seems to be due to the absence of hemolysin rather than of complement. Only a small percentage of the serums may be reactivated after heating by the addition of complement. This is due to masking rather than to destruction of the hemolysin. A distinct but not type-specific inhibitory effect could be demonstrated by the addition of heated serum to the active serum and cells. Isohemolysins behave like natural heterohemolysins and immune heterohemolysins in regard to absorption by their specific cells in the cold and their dependence on complement. No concentration by precipitation methods could be demonstrated. No hemolysin for corpuscles containing the C factor could be demonstrated. No hemolysis or agglutination was observed in testing serums of groups A, B, and AB against cells of group O.

AUTHORS' SUMMARY.

CUTANEOUS IMMUNIZATION AGAINST THE STREPTOCOCCUS OF GUINEA-PIG LYMPHADENITIS. L. D. HERTERT and K. F. MEYER, J. Infect. Dis. **44**:489, 1929.

The streptococcus of guinea-pig lymphadenitis has been used in the study of local immunization leading to the following conclusions: no protection could be demonstrated by means of Besredka filtrates; the portal of entry could not be closed by means of single or multiple injections of heat-killed streptococcic vaccines, and no local nonspecific resistance could be induced by intradermal injection of sterile broth or salt solution.

AUTHORS' SUMMARY.

CUTANEOUS IMMUNIZATION AGAINST *B. AERTRYCKE* IN THE GUINEA-PIG. HAROLD L. AVERILL and K. F. MEYER, J. Infect. Dis. **44**:495, 1929.

The intracutaneous injections of sterile antiviral containing specific filtrates may protect guinea-pigs within twenty-four hours against a fatal intracutaneous injection of highly toxic *B. aertrycke* in the same area. Some protection may be secured by subcutaneous injection of antiviral provided the massive infective dose is introduced not sooner than from forty-five to seventy-two hours after treatment. Similar experiments with Friedländer's bacillus and *Vibrio septique*. *Clostridium chauvæi*, gave negative results.

Guinea-pigs are protected on the eighth to tenth day after intracutaneous injections with specific filtrates or vaccines against subcutaneous or oral infections. These experiments indicate that the skin possesses special immune biologic properties for bacteria.

AUTHORS' SUMMARY.

HEMOGLOBINURIA AND URTICARIA FROM COLD. KENNETH E. HARRIS, THOMAS LEWIS and JANET M. VAUGHAN, Heart **14**:305, 1929.

Hemoglobinuria occurring in response to exposure to cold was found to be due to an hemolysin in the patient's serum. The skin reaction following the exposure was caused by a dermolysin in the patient's blood which at low temperatures united with the skin cells causing increased permeability and discharge of their contents. This is similar to what happens to the red blood cells in producing hemoglobinuria. Possibly certain cases of Raynaud's disease should be included in this category, gangrene being due possibly to a more intense action of the lysin on the skin. The dermolysin and hemolysin may occur singly or in combination as do also the hemoglobinuria and the urticaria.

PEARL ZEEK.

THE MEINICKE REACTION IN CONVALESCENTS FROM DIPHTHERIA. H. HENTSCHEL and L. SZEGÖ, Klin. Wchnschr. **8**:1395, 1929.

Micro-Meinicke reactions in children with diphtheria became positive by the eleventh to fifteenth day following antiserum injections in 81 per cent of the serums tested. There seems to be no relation between such positive reactions and serum sickness. Positive Meinicke reactions have been observed also with other diseases following serum injection. The serum reactions become negative gradually after several weeks. Other serologic tests for syphilis such as the Wassermann and the Sachs-Georgi react in much the same way following immune serum injections.

EDWIN F. HIRSCH.

DIPHTHERIA IMMUNIZATION WITH TOXIN-ANTITOXIN FLOCCULES ACCORDING TO H. SCHMIDT. MAX SOLDIN, München. med. Wchnschr. **76**:1208, 1929.

Children are rendered immune toward diphtheria by a single injection of 1 cc. of toxin-antitoxin floccules. For nurslings 0.5 cc. at the age of 6 months is recommended.

AUTHOR'S SUMMARY.

IMMUNITY AGAINST TUBERCULOUS SUPERINFECTION. B. LANGE AND K. LYDTIN, *Ztschr. f. Hyg. u. Infektionskrankh.* **110**:209, 1929.

By the inoculation of minimal doses of a certain strain of attenuated tubercle bacilli it was possible to produce in a guinea-pig with great regularity a form of tuberculosis which remained local for a long time. Guinea-pigs that had been prepared in this manner showed a certain degree of protection against superinfection with minimal doses of virulent bacilli if the superinfection was produced five weeks or later after the primary infection. The protection was greater than that afforded by cultures B.C.G. of Calmette, but it was less than that afforded by previous inoculation with a virulent strain of tubercle bacilli. It seemed as if the protection was proportional to the degree of tuberculous disease that was present in the inoculated animals. In either case the resistance produced was only a slight one.

W. OPHÜLS.

ON THE AGGLUTINOGEN PRODUCED FROM RED CORPUSCLES BY BACTERIAL FERMENT. V. FRIEDENREICH AND T. THUNE ANDERSEN, *Acta path. et microbiol. Scandinav.* **6**:236, 1929.

The specificity of this agglutinin, which was discovered by Thomsen, is confirmed. It has been demonstrated in the corpuscles of all the species examined and also in certain of the organs. It is regarded as a newly formed substance—receptor T—and its relation to iso-agglutination is discussed.

Tumors

MALIGNANT EPITHELIAL TUMORS OF THE NECK OF UNKNOWN ORIGIN. J. E. MCWHORTER, *Ann. Surg.* **90**:1, 1929.

Twenty-four cases of tumors about the angle of the jaw furnish the subject of this article. The masses are described, grossly, as firm, smooth or lobulated and usually encapsulated tumors situated in the deep tissues with freely movable skin overlying them. Histologically, they are composed of more or less undifferentiated epithelial cells which are similar to squamous epithelium but are frequently of a more embryonal type. An alveolar arrangement or a tendency to form sheaths of varying widths is not an unusual picture. They are frequently diagnosed as Hodgkin's disease or lymphosarcoma. No cysts are found and therefore the author concludes that they are not of branchiogenic origin. The usual tumors involved in this differential diagnosis are discussed.

RICHARD A. LIFVENDAHL.

THE EFFECT OF PARATHYROID HORMONE AND INCREASED CALCIUM METABOLISM ON THE GROWTH OF TUMOR TISSUE. A. GOERNER AND B. J. P. SHAFIROFF, *J. Cancer Research.* **12**:294, 1929.

The effect of parathyroid extract and increased serum calcium has been studied on the growth of Flexner rat carcinoma and the Crocker Fund sarcoma no. 10. The calcium content of the Flexner tumor has been increased but no inhibitory effect due to calcium was effected. The growth chart, which shows the tumor to be rapidly growing, and three cases of metastases are recorded. The calcium content of sarcoma no. 10 has not been increased—no difference of growth from the control being recorded.

AUTHORS' SUMMARY.

THE CARBOHYDRATE METABOLISM OF TUMORS (GLYCOLYSIS OF TUMOR TISSUE IN THE LIVING ANIMAL). C. F. CORI AND G. T. CORI, *J. Cancer Research.* **12**:301, 1929.

Cori and Cori report their experiments on glycolysis (the splitting of dextrose into lactic acid) of tumor tissue in vivo. Their ingenious technic was given in a

previous paper. In brief, a sarcoma was established on one wing of a chicken, and the venous blood leaving the tumor was compared with the venous blood from the normal wing. The blood that had passed through the tumor contained on an average 16 mg. per cent more lactic acid and 23 mg. per cent less dextrose than the blood that had passed through the tissues of the normal wing. Once this fact was established, they attempted to determine the rate of lactic acid formation of the tumor in the living animal in a quantitative way. They have obtained the following results: Rats with tumors weighing from 14.2 to 21 per cent of their body weight showed a marked increase in the lactic acid content of the blood. When the tumors corresponded to less than 10 per cent of the body weight, the lactic acid content of the blood was within normal limits.

They also found that the intravenous lactic acid tolerance of tumor-bearing rats was decidedly lower than that of normal rats and the decrease in tolerance was fairly proportional to the size of the tumor. By determining the difference in the lactic acid tolerance between normal and tumor-bearing rats, it was possible to arrive at an estimate of the rate of lactic acid production of the tumor tissue in the living animal. The values obtained varied between 570 and 800 mg. of lactic acid per gram of fresh tumor per hour, with an average of 690 mg. It is interesting that the rate of glycolysis of the tumor *in vivo* depends on the blood sugar concentration. At a normal blood sugar level of the tumor-bearing animals the glycolysis corresponds to one-half the maximal possible glycolysis of the tumor. The intravenous dextrose tolerance of tumor-bearing rats is the same as that of normal rats.

B. M. FRIED.

A CYSTICERCUS CARCINO-OSTEOCHONDRO-SARCOMA OF THE RAT LIVER WITH MULTIPLE CYSTICERCUS SARCOMATA. F. D. BULLOCK and M. R. CURTIS, *J. Cancer Research* 12:320, 1928.

Bullock and Curtis were the first to note that when rats are fed with *Cysticercus fasciolaris*, the larva of the cat tapeworm, *Taenia crassicolis*, they develop malignant connective tissue tumors of the liver. No adequate hypothesis has as yet been proposed to explain the lack of response on the part of the hepatic cells or the bile duct cells to form new growths under the influence of the same parasite. This is the more interesting in connection with the fact that in man *Paragonimus* frequently causes hepatic cancers.

In the present paper, the authors report a detailed study of a chondroma or chondrosarcoma and of a mixed tumor which they found in a rat infested with *Cysticercus fasciolaris*.

B. M. FRIED.

LOCAL INJURY AS A POSSIBLE CAUSATIVE FACTOR IN SARCOMA. E. BRADLEY, *Brit. M. J.* 1:599, 1929.

A railway signalman, aged 45, was well on April 19, 1928; when he pulled over a heavy signal lever with his left hand while his head was turned fully to the right, he felt something snap in the left side of his neck and had severe pain. On April 21, a physician noted a tumor, the size of a hazelnut, under the middle of the left sternomastoid muscle. The tumor increased rapidly in size but the man worked until May 4. On May 13, there was a brawny induration of the left side of the neck from the mandible to the clavicle and from the larynx to the edge of the trapezius muscle. On May 24, an operation was performed in an attempt to relieve the pressure on the larynx; death from cardiorespiratory failure occurred twelve hours later. At autopsy an unencapsulated conical mass, 4 inches (10.16 cm.) wide at the base and 6 inches (15.24 cm.) high, was removed from the neck. Microscopically, it was a highly malignant endothelial sarcoma. The trauma was regarded as a probable factor if not in causing the tumor, at least in having accelerated its growth.

GEORGE RUKSTINAT.

ON THE ACTION OF A GENERAL FACTOR IN THE DEVELOPMENT OF TAR CANCER IN WHITE RATS. BRUNO POLETTINI, *Tumori* **3**:306, 1929.

On the basis of his personal researches and those of others, the author comes to the conclusion that in causing experimental cancer in rats tar acts not so much as an irritating factor, as by profoundly modifying the general state of the organism of the animal in such a way as to produce a true predisposition to tumor growth.

W. OPHÜLS.

THE INTERCELLULAR BRIDGES AND THE GENESIS OF CARCINOMA. A. KREIKER, *Virchows Arch. f. path. Anat.* **271**:724, 1929.

This study is based on thirty-eight cases of basal cell carcinoma of the face. In more than half of them a nevus verrucosus preceded the carcinoma. The usual theories concerning the cancer cell assume a biologic change within the cell which makes the cell a foreigner to the organism. This seems biologically impossible. In the theory brought forward by the author, such an assumption is unnecessary. Carcinoma (of the skin) is formed when isolated basal cells are unable to form a closed system again. Normally, all skin epithelium forms one mechanical system, the cells being united by the intercellular fibrils. When a trauma, for instance, isolates a group of cells, the isolated cells will multiply until they have formed a new system or have become reunited with the skin epithelium. The intercellular fibrils represent the anatomic basis for the growth restraint of skin epithelium. A frequent form of a new closed system formed by isolated skin epithelium is the cyst; it does not grow any more, it only becomes distended. The best example for absence of a closed system is the tissue culture with its unrestrained growth. The fact that in basal cell carcinoma all cells are connected with each other explains the absence of metastasis. The ulceration is due to the absence of the protecting hornified layer; it does not prove the destructive power of the tumor cells.

ALFRED PLAUT.

ON TAR CARCINOMA WITH LONG LATENT PERIOD. R. ZENKER, *Ztschr. f. Krebsforsch.* **28**:121, 1928.

In a rabbit that had been subjected to repeated application of tar to the ear over a long period, the initial hypertrophic changes disappeared almost completely after the cessation of the applications, but two years after this there developed the usual tar carcinoma. Evidently, the processes initiated by a temporary irritation may persist with eventual development of malignancy—a phenomenon observed in human beings in the carcinomas of aniline and paraffin workers.

H. E. EGGERS.

CONTRIBUTION TO THE PATHOLOGY OF ATYPICAL GRAWITZ TUMORS. F. SCHAFFHAUSER, *Ztschr. f. Krebsforsch.* **28**:131, 1928.

On the basis of a fully described tumor of the Grawitz type, apparently primary in the kidney, which showed marked metaplastic development in the form of recognizable tubules, alveoli of vacuolated cells, sarcoma-like portions and giant cells, the writer concludes that the most logical explanation of the so-called hypernephromas is that they originate in undifferentiated embryonic tissues, with potentialities toward both suprarenal and renal development.

H. E. EGGERS.

ON THE TAR CANCERS OF BRIQUET WORKERS. TEUTSCHLAENDER, *Ztschr. f. Krebsforsch.* **28**:283, 1929.

In a study of the tar cancers of briquet workers made in Baden and South Wales, the author arrives at the following conclusions: The cancers are of the ordinary squamous epithelial type and do not differ in their behavior from similar carcinomas of other origin; the briquet dust appears to be the irritative agent, possibly also the vapors arising in the course of briquet manufacture. These

carcinomas are of frequent occurrence, but seldom appears in less than five years' exposure; after this period tar warts are practically constant. Preventive measures are urged: the preferential employment of young persons, the frequent changing of labor personnel, avoidance of personnel with already diseased or unduly sensitive skin, avoidance of persons who will not observe rules of personal cleanliness or prophylaxis, publication and explanation of prophylactic rules, supervision of their enforcement and moistening of the dust.

H. E. EGGERS.

STUDIES OF THE HISTOGENESIS OF ROENTGEN TUMORS OF PLANTS. KOMURO HIDEYO, *Ztschr. f. Krebsforsch.* **28**:371, 1929.

In developing roentgen tumors of the root tips of pea seedlings, the writer describes filiform structures resembling closely what have been described as nerve filaments in experimentally induced tumors in animals.

H. E. EGGERS.

TAR CANCERS IN VITALLY IMPREGNATED MICE. J. G. SANCHEZ-LUCAS, *Ztschr. f. Krebsforsch.* **28**:374, 1929.

Tar cancers were found to develop in mice that had been impregnated with India ink by intravenous or intraperitoneal injection, in splenectomized mice and in mice subjected to both procedures, to the same degree as in untreated animals. There were no noteworthy differences shown in the microscopic examination of the internal organs.

H. E. EGGERS.

THE HISTOLOGIC SIMILARITY BETWEEN EPITHELIAL REGENERATION AND CANCER FORMATION. H. MUELLER, *Ztschr. f. Krebsforsch.* **28**:383, 1929.

The author is an advocate of the theory that epithelial regeneration occurs not from epithelial cells themselves, but from undifferentiated elements originating in close association with subepithelial capillaries. According to his view, carcinoma is the result of repeated destruction of epithelial cells, with liberation from them of hormone-like substances which stimulate the undifferentiated elements to excessive and eventually unrestrained reproduction of the destroyed cells. He believes that he has evidence for the view that metastatic growth is really accomplished by mesenchymal elements stimulated to the formation of epithelial cells by the hormones reaching the new site from the primary location.

H. E. EGGERS.

ON A CASE OF CANCER FOLLOWING A BURN. H. STAUFFER, *Ztschr. f. Krebsforsch.* **28**:418, 1929.

Stauffer reports a case of facial carcinoma following a local burn incurred thirty days before. The surrounding noncancerous skin showed marked senile precancerous hyperkeratosis.

H. E. EGGERS.

SPONTANEOUS TUMORS OF MICE AND THE ETIOLOGIC ASPECTS OF THE CANCER PROBLEM. L. HEIDENHAIN, *Ztschr. f. Krebsforsch.* **28**:443, 1929.

Since Haidenhain's experimental results have been explained on the basis of spontaneous tumor development, he discusses in this article the incidence of such tumors. In his experimental material, his frequency of tumor development was of the same order as that observed by Maude Slye in her work on the genetics of tumor. Unlike her tumors, those obtained by him showed no particular affinity for certain organs, and a number of them were located in regions in which spontaneous tumors are very rare in the mouse. From such information as he was able to gather, the relative frequency in Germany of spontaneous tumor development in mice is about 1.4 per cent—a figure far less than that obtained by him experimentally.

H. E. EGGERS.

RESULTS OF THE CYTOLOGIC STUDY OF TUMORS. B. LIPSCHÜTZ, *Ztschr. f. Krebsforsch.* **28**:491, 1929.

Using Giemsa's stain in carefully selected material, the writer has found in the cells of Rous' sarcoma intracellular inclusions of the same general order as those found in diseases caused by known filtrable viruses. In view of the numerous other similarities between the filtrable agent of Rous' sarcoma and those viruses, he concludes that the demonstration of these bodies places this agent among the filtrable infections.

H. E. EGGERS.

THE DEVELOPMENTAL STAGES OF THE EPITHELIAL CHANGES PRECEDING SKIN TAR CANCERS. A. BABES, *Ztschr. f. Krebsforsch.* **28**:533, 1929.

The precancerous changes in the skin of the rabbit's ear following application of coal tar vary according to the mode of application, one series of changes following the simple swabbing of the surface, another the deep introduction of the tar by rubbing. With the former there is first an atrophy of the hair follicles and sebaceous glands, but with persistence of their surface openings, which dilate into saclike invaginations from which there is an outgrowth of epithelial buds. Between the sacculi there is hypertrophy of the skin, either diffuse or in the form of buds. As the sacs deepen, the skin assumes a papillary surface relationship, without anything atypical in the overgrowth except hyperkeratinization. With the deeper introduction there is complete destruction of hair follicles and glands, with regeneration of these elements in the form of epithelial processes which gradually grow deeper and cornify. There is a great resemblance of these changes to senile hyperkeratosis.

H. E. EGGERS.

Medicolegal Pathology

METHYL CHLORIDE POISONING. A. H. KEGEL, WILLIAM D. McNALLY and A. S. POPE, *J. A. M. A.* **93**:353, 1929.

This article reviews briefly the literature in question and discusses the symptoms and changes in the organs caused by methyl chloride gas in high dilutions. The interest in poisoning from this gas is acute in Chicago at this time on account of the occurrence of a considerable number of deaths from the escape of methyl chloride gas in kitchenette apartments from leaks in the apartment units. Undoubtedly, instances of poisoning have occurred without being recognized as such. The principal symptoms appear to be drowsiness, mental confusion, nausea, vomiting, coma and, in severe forms, convulsions. The lesions consist of parenchymatous degeneration, multiple hemorrhagic extravasations and pulmonary congestion. The clinical sequelae suggest progressive degenerative processes in the central nervous system.

RECENT ADVANCES IN TOXICOLOGY AND FORENSIC MEDICINE. SIR WILLIAM WILCOX, *Lancet* **2**:970, 1927.

At a meeting of the Medico-Legal Society of London on Oct. 27, 1927, Sir William Wilcox, in discussing some of the ways in which toxicology assists the law, referred at some length to arsenic; the arsenobenzene compounds; the improved methods for detecting alkaloids; the differences in the symptoms of poisoning from lead when given intravenously as is done for cancer, and the usual symptoms of poisoning from this metal, and to the huge number of new drugs, especially the hypnotic remedies and the 257 deaths (from 1905 to 1925) from the barbituric acid group. He also mentioned the liver poisons, tetrachlorethane, trinitrotoluene, dinitrobenzene, picric acid and dinitrophenol, and the toxic jaundice and subsequent cirrhosis that they cause. He also spoke briefly of the advances made in the study of blood stains, particularly blood grouping and the interest recently displayed in Great Britain in wounds from fire-arms, more especially

since Professor Sidney Smith gave so much attention, when in Cairo, Egypt (now in Edinburgh), to the identification of bullets by marks that they receive from the barrels through which they are fired.

E. R. LeCOUNT.

INFANTICIDES BEFORE THE INFANTS HAVE BREATHED. M. E. SOREL, *Ann. de méd. lég.* 8:515, 1928.

There are many reports of infants killed by a kick or blow on the head, strangulation or even decapitation before they had a chance to breathe and with only the head born. As a consequence, pulmonary docimasia, tests to determine whether the child has breathed or not, although very important, are by no means final in deciding whether infants are born alive. Sorel reports two cases of live birth, one of them first known when the mother confessed having killed the infant before it made a noise, by wounding the hard palate with a finger or fingers in the mouth when she suffocated the infant. The other infant was strangled with a strip of ticking and there were hemorrhages in the outer layers of the wall of the left carotid artery where the cord had bruised the vessel. Thorough examinations in various ways failed to disclose any evidence of aeration of the lungs of either child.

E. R. LeCOUNT.

TRAUMA AND TUBERCULOSIS. L. DESCLAUX, *Ann. de méd. lég.* 8:518, 1928.

In order to prevent an awning from falling the left hand of a young girl who was helping lift it was so severely twisted on her forearm that the wrist swelled and was painful. Six weeks later tuberculosis was found of the left carpal bones. A maximum of a year of disability was fixed as the basis of compensation. Discrete lesions with dulness were found in the apex of the left lung. The opinion was given that the bones of the wrist were tuberculous at the time of the accident and the torsion had brought on a more rapid development of the fungous osteoarthritis.

E. R. LeCOUNT.

INFANTICIDES AND ABORTIONS IN WARSAW SINCE THE WORLD WAR. W. GRZYWO-DABROWSKI, *Ann. de méd. lég.* 8:545, 1928.

INFANTICIDES IN EUROPEAN RUSSIA. N. W. POPOFF, *Ann. de méd. lég.* 8:532, 1928.

This is a detailed account full of statistics of the increase of abortions, infanticides and deaths of the mothers from puerperal sepsis in Warsaw in the eight years between 1918 and 1925, also of the apathy of the public and the leniency of the law regarding them. Based on the numbers of abortions in Paris before the war, 50,000 each year for 3,000,000 inhabitants, and those in Lyon at that time, 10,000 a year for a population of 500,000, the number in Warsaw is said to be at least 15,000 for its population of 1,000,000. Calculations from other sources place the abortions in Warsaw as 1 for every 5 pregnancies. The ratio to births for four years is as follows:

Year	Births	Abortions
1921.....	21,710	4,991
1922.....	22,980	5,285
1923.....	22,701	5,451
1924.....	21,157	4,866

Estimates made from the number of women treated in hospitals for the complications following abortions, the number of postmortem examinations and court statistics all were found corroborative of the increase of abortions and of infanticides.

At the Medico-Legal Institute in Warsaw in these years, from 1921 to 1925, 1,043 bodies of infants born at term or prematurely were examined, 483 stillborn and of these only 13 per cent at term; 142 infanticides or deaths from violence and of these 85 infanticides by asphyxia in one way or another. There were

20 bodies of infants born at term in which cranial fractures were found; 48 were born at term and died solely from lack of proper care at that time, and 117 were nonviable, etc.

During the years from 1918 to 1925, examining magistrates inquired into 141 cases of infanticide. In 47.7 per cent the women were acquitted; in 18.5 per cent condemned, but frequently with a reprieve; in 35.7 per cent the accused was condemned for failure to bury the body of the fetus or infant. Among cases tried for abortion from 1920 to 1924 inclusive, the mothers were implicated in 45 and of these women 16 were convicted and 39 set free. There were 51 midwives tried during this same period and 16 were convicted. In higher courts, of 118 who were tried for abortion, 58 were convicted. The deaths of mothers from abortion and its sequences rose steadily from 18 in 1921 to 43 in 1926. Popoff, Professor of Legal Medicine in Smolensk, reckons that the increase in infanticide, defined in Russia as murder of the infant by the mother at the time of birth, increased from 2.7 per ten thousand births in 1909 to 6.7 in 1925, the total number being 376 in 1909 and 1,120 in 1925. For the years from 1913 to 1919 inclusive, information is not available.

E. R. LECOUNT.

INDUSTRIAL DISEASES. G. ROUSSELIER, *Ann. de méd. lég.* 8:553, 1928.

In a military pharmacy three employes were found affected by drugs with which they were employed. One was sensitive to quinine and suffered with engorged blood vessels of the head and neck resembling impetigo or an eczema; these were much worse if the patient was menstruating. Another had eczema whenever she worked with emetine; a third woman had eczema from powdered pyrethrum. Another laborer suffered from an acute poisoning from handling crude nux vomica; four others painful conjunctivitis from asphalt, and others local lesions from cement used in making tiles. These are all mentioned as unusual disorders from occupations with which the customary legal awards for damage and disability have had, as yet, but little to do.

E. R. LECOUNT.

EXPLOSION IN A STARCH FACTORY. J. LECLERCQ, C. VALLÉE and M. MULLER, *Ann. de méd. lég.* 8:581, 1928.

In describing the conditions accompanying and results from the explosion of a starch factory near Lille in which seven persons were killed and thirty-seven wounded, eight of these severely, the position of some of the bodies is described and illustrated as follows: extremities shrivelled, thighs flexed on the pelvis, legs flexed on the thighs, forearms flexed on the arms, the hands and fingers flexed and in front of the chest in the attitude taken by boxers. The red blood corpuscles in the capillaries of the lungs were found carbonized by a microscopic examination.

E. R. LECOUNT.

STAINS ON CLOTH MADE BY BLACK POWDER. PIÉDELIÈVRE and SIMONIN, *Ann. de méd. lég.* 8:615, 1928.

By using crockery ware, shaggy cloth, white linen, sheets of rubber, animal skin, etc., as targets and removing the metal bullets so as to leave simply the powder, it was proved that the black rings with white centers made by black powder shot against certain fabrics are due to a rebound of the cloth. Such marks are not made on the skin, nor are they made by smokeless powder.

E. R. LECOUNT.

TRAUMATIC DIABETES. G. ROUSSELIER, *Ann. de méd. lég.* 8:617, 1928.

Injuries of the cerebrospinal axis sustained by two persons were followed by diabetes. One was a man, aged, 65, who was debilitated; the sugar was never more than 2 Gm. in twenty-four hours and disappeared altogether after a few months. There was no glycosuria twenty days before the accident, which among

other injuries included a wound in the right temple, 4 cm. long. In the second case, it was admitted that glycosuria might have been present before the accident. Compensation based in some part on traumatic diabetes was secured by both patients. Roussellier mentions about fifty other patients in whom injury was followed by a great variety of definite lesions of the brain, but without glycosuria. He believes that traumatic diabetes is exceedingly rare.

E. R. LeCOUNT.

ASSAULT WITH LIGATION OF THE PENIS. P. MULLER, *Ann. de méd. lég.* **8**:620, 1928.

A boy, aged 8 years, fearing punishment, managed to keep secret his ligated penis until after departure of his father the next morning, when it was discovered by his mother. It was necessary to call a surgeon to sever the cord deeply buried in the penetrated base of the prepuce. The scrotum and loose tissues about the bladder were infiltrated with urine of which a large amount escaped when the cord was cut. Gangrene for 4 by 7 cm. of the scrotum followed, but about three months later the parts were normal.

The boy accused two other boys of attacking him, one of 12 holding him down while the other, about his own age, tied his penis. This the boys denied and they were released from custody. The case was then carried to a higher court, and in spite of an opinion given by Muller that the boy could not have tied his penis in the way it was found, they were again released. The report illustrates the difficulty of legal dealings with children. In discussing this, Brisard told of complete severance of the urethra from a ligature of the base of the penis of a boy of 7 or 8 years which the boy himself had applied.

E. R. LeCOUNT.

DEATH FOLLOWING PUNCTURE OF THE CISTERNA CEREBELLOMEDULLARIS, H. STEINDL, *Deutsche Ztschr. f. Chir.* **209**:97, 1928.

In place of obtaining colorless, thin, cerebrospinal fluid when the cisterna was punctured to relieve pressure, blood poured forth in a pulsating stream and after death the left vertebral artery was found punctured. From the perforated artery blood accumulated beneath the dura at the base of the brain. A carcinoma of the pharynx had invaded the brain and although trephining, and also many lumbar punctures, had already been done to relieve pressure, it was thought that puncturing the cisterna would relieve the headaches. The artery was wounded because the cisterna was empty and the medulla was displaced back and to the right bringing the left vertebral artery into the line of puncture. Death did not occur until four days after the puncture.

E. R. LeCOUNT.

ANEURYSM OF THE AORTIC ARCH FOLLOWING A WOUND WITH SHRAPNEL. R. NISSEN, *Deutsche Ztschr. f. Chir.* **211**:262, 1928.

Shortness of breath, considerable expectoration and subcutaneous emphysema all appeared rather abruptly two weeks after a man, aged 36, was wounded with shrapnel in 1916. The ball entered behind between the shoulder blades. During the third week, a left thoracentesis yielded blood and there were abnormal heart sounds affecting all the valves. He returned to the war front in 1917, and to his occupation as carpenter after the war. Because of pain in the thorax, an examination in 1920 revealed the shrapnel ball, and he obtained 20 per cent of the total disability pension. His work was not heavy for three years after this, but he returned to his carpenter work at the end of this period whereupon the former symptoms returned. In 1927, his pension, then 30 per cent, was considered again and by another examination an aneurysm was found at the aortic arch, the shrapnel ball in the posterior mediastinum moving with each heart beat; the pension was increased to 66.66 per cent.

E. R. LeCOUNT.

SUICIDE AS A RESULT OF BODILY SUFFERING. K. MEIXNER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **12**:133, 1928.

To refute the rule that persons who kill themselves are mentally diseased two suicides are reported of persons who, it is assumed, were in great pain at the time. In the body of one, death by stabbing, a fresh coronary thrombosis was found; in the other, a perforated gastric ulcer with peritonitis, death by shooting.

E. R. LECOUNT.

CONCERNING KNIFE WOUNDS. H. MERKEL, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **12**:137, 1928.

This is an entertaining account of unusual experiences with stab wounds and of the exceptional peculiarities such wounds may possess. Of three deaths caused by falling on or against knives accidentally, one was of a man who carried a naked knife in one hand and had a fall when riding a bicycle through woods where he feared he might be waylaid. Cuts across the throat, causing the death of a girl, aged 15 years, were obviously made from the left side. It was known that she was right-handed but further inquiry and another examination of the body disclosed that her right hand had been injured some days before. The first suspicions of assault and murder were then dismissed. Some time subsequently, the father admitted that he had punished her for remaining out late just before she had cut her throat. The weapon, a razor, was found by her head and it was concluded from the way the blood was distributed on her clothing and surrounding objects that she inflicted the wounds while kneeling.

Three deaths from stab wounds, deeper than the length of the blades with which they were made, were explained by the force used which drove in the outer parts after they were pierced. In a fourth, the discrepancy between the two, length of blade and depth of wound, was too great and further search resulted in finding a second weapon with a longer blade and its identification as the one used. The most remarkable of the ten cases reported deals with the dead and greatly decomposed body of an unknown woman found in a thicket. A meshwork of vegetation had grown through some of the clothes. When identification was made and it was decided that cuts into the front of the body of the third cervical vertebra represented the bottom or deepest part of wounds across the throat when she was murdered, the affair was easily terminated. She had disappeared about a year previously. The apprehended murderer confessed and was sentenced to death, but subsequently this was changed to imprisonment for life.

E. R. LECOUNT.

IDENTIFICATION FROM PORTIONS OF BODIES. RAESTRUP, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **12**:176, 1928.

This prosaic account, illustrated by a number of cases, deals with mistakes in the identity of dead bodies, disputes over the identity and the unreliability for purposes of identification of clothing, letters, laundry marks and similar objects found on or with bodies of persons unknown. Publicity of descriptions and photographs of such bodies are the best means of securing identification. Raestrup describes at considerable length measures which when taken result in lifelike photographs. Substances may be injected into the loose orbital tissues to push the eye balls forward; gritty powder underneath the eyelids will hold them open; the sagging mandible may be held forward by sewing the jaws or teeth together in front, and entire faces with glass eyes may be built up from merely the bare skull. Considerable difficulty is met with in identifying burned bodies, but even with these identification is often successful from tattoo marks, matters of dentistry and sometimes finger prints.

E. R. LECOUNT.

ACCIDENT OR HEART DISEASE. W. BRANDIS, *Med. Klin.* **24**:424, 1928.

After opposing expert opinions were obtained from professors in two pathologic institutes, it was decided by officials who pass on matters of insurance for the

government that an occupation was not responsible for the death of a man, aged 48, who died from heart disease. In his work he had occasion to press against machinery with his chest and calluses formed where the upper right ribs join the sternum. The enlarged heart was not explained satisfactorily either during life or after the postmortem examination. The coronary arteries were sclerosed; no mention was made of blood pressure or of histologic examination of the myocardium.

E. R. LeCOUNT.

CHRONIC BENZENE POISONING: ONE DEATH. K. LANDÉ and L. KALINOWSKY, *Med. Klin.* **24**:655, 1928.

An eczema of the hands and arms, slight changes in the blood, hemorrhage from the nose and gums and later a severe degeneration of the left median nerve with atrophy of the muscles it supplies were the chief symptoms of a man exposed to the vapors of benzene where as many as 15,000 or 20,000 liters were transformed from tanks to cars; his hands were also kept wet with the benzene. The illness occurred after he had this occupation for one year.

The other man worked for two years, applying to automobiles lacquer or varnish in a 40 per cent solution of benzene. His symptoms came on with weakness for about six months before death, loss of appetite and emaciation, and later, hemorrhage from the nose so severe that he finally came under medical observation. At this time the hemoglobin was 36 per cent, but before death it sank to 17 per cent; the red cells numbered only 1,000,000. He also had fever, which has been noted a few times in other patients, with chronic benzene poisoning and has been laid to tissue destruction.

He lived only eight days after entering the hospital, and at postmortem examination the bone marrow was found to be aplastic. Both these patients had a mild leukopenia, gingival hemorrhages and severe bleeding from subcutaneous blood vessels after trivial bruising. The authors claim that the monoplegia is the first to be reported from benzene.

E. R. LeCOUNT.

FATAL HEMORRHAGE FROM A MINUTE ULCER OF THE STOMACH. H. NAUMANN, *Med. Klin.* **24**:935, 1928.

A woman, aged 22, after a few prodromal symptoms diagnosed as mitral insufficiency, had bleeding from the stomach and bowel which was unexplained during life and after death until by careful search a minute gastric ulcer was found with an eroded thrombosed artery stump in its center, the vessel being about as large as a fine hair.

The bleeding continued over at least seven days, but probably lasted much longer because when she first came under observation the hemoglobin was only 36 per cent; just before death it was 17 per cent. There was no evidence of the ulcer in the outside of the stomach, and for this reason an operation probably would have been of little use.

E. R. LeCOUNT.

COMPLETE TEAR OF THE RIGHT SUBCLAVIAN ARTERY IN TRAINING FOR ATHLETIC SPORTS. W. KOCH, *Med. Klin.* **24**:1473, 1928.

A man, aged 22, an all-round athlete, suffered from pain in his right shoulder and chest after swimming with a breast stroke. After a physician had massaged his heart, for he had an hypertrophied heart with some mitral insufficiency, he exercised at home with an "Expander" loaded with a weight of 110 pounds. During this exercise, he was suddenly seized with severe pain as before in the right shoulder and right side of the chest, which also extended down the right arm; soon after, nausea, difficulty in swallowing and air hunger obtained.

He collapsed suddenly on the street five days after return of the pain, became unconscious and was taken to a hospital where at first perforated gastric ulcer was diagnosed. This was abandoned when 600 cc. of blood was removed from

the right pleural cavity; death occurred eight days later in the hospital very suddenly after a cry and the appearance of a bluish swelling in the right infraclavicular fossa and adjacent arm. After death the right subclavian artery was found torn completely across, 3 cm. from its origin, and the blood after dissection of the surrounding tissues had broken into the right pleural cavity where there was still 1 liter. Nothing is said by Koch regarding a cervical rib in his difficult explanation of how the tear was produced.

E. R. LeCOUNT.

HEART DISEASE AND ACCIDENT. W. HEIMANN-HATRY, *Med. Klin.* **24**:1596, 1928.

A woman who had fallen when 4 years of age and as a consequence suffered for many years from kyphoscoliosis of the spine and a deformed thorax, when 54 injured her chest in an automobile accident, breaking some ribs and one forearm. Directly after the accident she had symptoms of severe cardiac disorder: cyanosis, rapid pulse, many extrasystoles, a sense of cardiac compression and of impending death. She died unexpectedly about seven months later; a necropsy was not done. The opinion is expressed that the internal injuries hastened death from heart disease in one already greatly afflicted with compressed thoracic viscera.

E. R. LeCOUNT.

ACCIDENT, HEART DISEASE OR RENAL DISEASE. W. BRANDIS, *Med. Klin.* **24**:1633, 1928.

This is a review by one of the officials, a judge, who decide questions of liability for insurance of employes and includes the observations and opinions of the physicians attending the deceased, as well as the reports of directors of two pathologic institutes whose expert opinions were sought. Claim by the widow for compensation for the death of her husband was denied because the disease of the left kidney from which it was alleged death had resulted was part of a systemic infection and not due to accident.

The man complained of pain and of having torn some muscle of the abdominal wall when lifting a heavy piece of iron. A few days later he died of an infection, thought at one time to be "grippe." At postmortem examination, a thrombo-ulcerative aortic endocarditis was found with embolic hemorrhages and infarcts in both kidneys and the spleen. The head was not opened; the renal lesions were multiple small infarcts and hemorrhages and included no abscess, as was claimed.

E. R. LeCOUNT.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Oct. 14, 1929

HENRY C. SWEANY, *President, in the Chair*

THE NECROPSY IN MEDICAL EDUCATION AND STUDY. PRESIDENT'S ADDRESS. HENRY C. SWEANY.

I wish to thank you for honoring me as you have on this the fiftieth year of the founding of the Chicago Pathological Society.

Custom dictates an address on this occasion. I have therefore prepared a discourse on pathology as a basic medical science, the purpose of which is to point out the deficiencies existing in our medical education, resulting from our relative lack of necropsy material.

I shall first scan a few centuries of medical history for fitting precedents. Beginning with the Renaissance period, relatively few of the outstanding characters need be mentioned to reveal the relationship of morbid anatomy to the progress of medical science. Before morbid anatomy could be studied, there had to be a knowledge of normal anatomy.

Vesalius (1514-1564), champion of anatomic dissection, boldly departed from Galenic dogma and the theories of his teachers to carry out his classic anatomic studies. Nevertheless, he laid the foundation of surgery which Pare, his contemporary, appreciated and made use of to help elevate medicine from the mediocrity of the barber.

Enthusiasm then waned gradually until the appearance of John Hunter in the eighteenth century, when a new impetus was given to all branches of medicine. As an experimenter in medical research, Hunter knew no limitations. His ambition was the solution of the unknown, whether in man or animal; in the field of anatomy, physiology, medicine or surgery. However, his greatest accomplishments were in surgery and experimental pathology.

Again, on the continent, at the end of the eighteenth century, anatomy and surgery received another stimulus as a result of the efforts of Bichat (1791-1802), a protege, student and friend of the surgeon Desault, whose chief claim to immortality is that he was Bichat's teacher.

During this time, internal medicine was plodding along as a semimystic cult, aided at first by the bombastic Paracelsus, but aroused completely by the immortal discovery of Harvey in the early seventeenth century. Two hundred years later saw it definitely established on physiologic principles by that versatile genius and teacher, Johannes Muller.

Even while surgery was being founded, through anatomic discoveries and internal medicine established on principles of physiology, a new science came into being. This afterwards became known as pathology, a synonym more practical but less expressive than the older morbid anatomy.

The first great work in this field, entitled "The Seats and Causes of Disease Investigated by Anatomy," by Morgagni, was published in 1761, more than 100 years after Harvey. This marked the true beginning of pathology in science. In the same year of Morgagni's publication, there was born a Scotchman, Matthew Baillie, who published the first complete textbook on pathology, and included case histories along with the autopsy records.

The scene again shifted to France where Bayle, Laennec and others created a lasting medical atmosphere by combining clinical manifestations with anatomic aberrations. Again utilizing morbid anatomy as a basis, Bright, Addison and Hodgkin markedly advanced the cause of medicine in England. This was followed

by the creation of the Viennese school by Rokitsansky, the pathologist, and Skoda, the clinician, whose combined influence created in Vienna one of the world's greatest medical centers and marked the climax of gross pathologic study.

Both medicine and surgery now veered into this new field of morbid anatomy for advancement. Following the cell theory of Schleiden and Schwann and the discoveries of the first great histologist, Henle, microscopic pathology became a field for exploitation. This was ably accomplished by the incomparable Virchow. Rudolph Virchow was the most conspicuous figure in the history of medicine of the second half of the nineteenth century, the most successful exponent of scientific methods of medical investigation and research, and the founder of modern pathology.

With his work, so-called "dead house" pathology became and remained the single most important means of medical education. It is the primary school of medicine, contributing the knowledge that furnishes the foundation for medical education. By it the practice of medicine has been lifted out of a tangled mass of superstition and cultism and established on the basis of an exact science.

During the latter part of this brilliant naissance, the Chicago Pathological Society had its modest beginning, an outgrowth of the West Chicago Medical Society. The first meeting was held in the "Old Washingtonian Home" May 13, 1878, Dr. Norman Bridge presiding. Three years later, it received its present name.

Among the reports of the society printed in the *Chicago Medical Journal and Recorder* of that time, were some by Christian Fenger, the first pathologist at the County Hospital and one of the first modern pathologists in America. In discussing this subject, Kektoen quoted from a report by Dr. Edward Holmes that the first autopsy performed in this part of the country was done by Fenger. Fenger, who had come from abroad, was implanting in the minds of medical men of this community the methods of the European schools. In fact, great pilgrimages to the European clinics began shortly after. It was during this time that Belfield brought back Koch's method for the demonstration of tubercle bacilli.

In the early nineties, laboratory methods were introduced and from that time the reports became more scientific. The "Society Transactions" were started in 1894, and the meetings were held in the central part of the city.

The development of pathology in Chicago proceeded under the industrious efforts of Hektoen, LeCount, Zeit, Klebs, Weaver, Herzog and later Wells, Davis and many others who carried on the work started by Fenger.

Most of our accomplishments, however, have not been in the fields that made Europe the center of medical learning. Bacteriology, under Pasteur, Klebs and Koch, drew a great deal of interest, while immunology, biochemistry and experimental pathology progressed with great strides in this country.

The pathological institutes, so prominent in Europe, have not fared so well. With the exception of LeCount's extensive necropsy experience, the volume of work in Chicago is not to be compared with that in Europe. LeCount's work in the Cook County coroner's office was chiefly suitable for individual study of pathology. By no means do I wish to detract from the unparalleled work in the newer sciences in this country, but I do hope to emphasize the advantage possessed by men who have enjoyed an extensive postmortem training in their medical education, and further emphasize that such training here, except in a few institutions, is far from satisfactory.

Despite the fact that necropsy work has more than doubled in Chicago in the last ten years, the number is far below that obtained abroad. The percentages for the year 1926, from the report of the Institute of Medicine, reveal that the necropsies by permission, not counting the necropsies in the County Hospital, represent 21.1 per cent of all deaths in the respective hospitals, while the figures from the *City Health Bulletin* for the same period, covering all deaths in the City of Chicago, give by calculation only 5.3 per cent necropsies by permission; that is, for every five deaths in the hospitals and every eighteen deaths in the city at large, there is one necropsy by permission. The New York Academy of Medicine reports that the ratio of necropsies done in hospitals in Europe to those in America is as 62.7 per cent to 7.3 per cent, almost 9 to 1, while Karsner places the number for the country at large at 0.7 per cent.

Different authors comment on these statistical variations, here and abroad, from several viewpoints. Lack of interest by physicians is considered the most important. Robertson cited a medical student who hoped that he would not be insulted by being asked for a necropsy on his deceased father. The same author maintained that this feeling is quite general among members of the medical profession. Smith stated that the laity at times are more appreciative of necropsies than physicians. Bell, Wilson and others are in general accord with these statements.

Pathologists especially should be willing to have themselves or members of their families examined postmortem, but unfortunately they do not all set this precedent. This is inexcusable, and Mills said that a conscientious physician has no moral right to ask permission for that which he would not permit for himself or a member of his family.

The causes of this condition vary with the reactions of different physicians, and may be grouped into four divisions. Some do not feel the need of a repetition of the pathologic observations on which they base their clinical diagnosis. For this class, it is well to point to the figures of Karsner which showed that, in a high class hospital, there were 8 per cent gross errors with 60 per cent minor errors, and those of Cabot who reported 47 per cent of diagnoses partially or wholly wrong, over a ten year period, in the Massachusetts General Hospital; also those of Oertel from a large public hospital where only 22.3 per cent of the diagnoses were entirely correct. Frances Carter Wood pointedly summarized the situation in saying that only the pathologist realizes how many patients with hysteria have tumors of the brain; in how many cases of heart disease there are no valvular lesions but nephritis; and that 10 per cent of all old people die of unsuspected cancer.

Another type of physician fears exposure of his ignorance. This class needs no comment further than that a few postmortem examinations in their earlier education would have better prepared them.

In the third group are those too busy or too mercenary to be troubled with postmortem examinations. For their benefit, let us point out that Sir William Osler, among other great physicians, cancelled all appointments to attend necropsies on his patients.

Finally, a fourth group are disinterested or indifferent. Here the pathologist is chiefly to blame. The postmortem service can be sufficiently attractive to interest any physician interested in improving his professional knowledge. The pathologist should gage his success not by the variety of material appearing before him, but by the increasing interest manifest in attendance and number of necropsies.

Next to the apathy of physicians is the lack of appreciation on the part of the public. A difference of opinion exists regarding the cause of popular objection to postmortem examinations. Wilson called it a lack of selfish interest on the part of the relatives to know the condition of the deceased as well as the light it may throw on the condition of the whole family. The reports of the New York Academy of Medicine lay it at the door of ignorance of the value which this procedure has for science and, therefore, for the human race. Consequent on this there is a universal lack of appreciation on the part of the American public.

This general feeling may be resolved into its elementary factors, most important of which is the "emotional." At the time of death, the high state of emotionalism in the family is not given consideration by the physician or the pathologist, to whom a necropsy is only a perfunctory task. This familial sentimentality is present and must be encountered in a sympathetic and tactful manner.

To the emotion of love, there is added a certain amount of fear that has been frequently attributed to religion. There still lingers in the minds of many people the medieval superstition about the dead.

So far as religious objection is concerned, it seems that this, per se, has been overemphasized. This attitude of fear concerning religion has no true foundation in any religious code, and nowhere can such reference be found. Personally, I have always found cooperation on the part of the clergy after a few words of

explanation. Bluestone, discussing this subject, insisted that religious objections are not hard to refute. He cited Father Moulinier, president of the Catholic Hospital Association for 1926, who pleaded for necropsies in hospitals and for the advantages gained from them. Although Schultz, Joslin, Karsner and others reported on the difficulty of obtaining permission for necropsies on Jewish patients, it seems more logical to assign the cause to familial ties than to religion.

Aside from the apathy on the part of the physician and the ignorance and emotionality of the public, a third and most important factor is the undertaker. In some communities, namely Minneapolis and Cincinnati, much assistance has been gained through the cooperation of the undertakers. Or they may hinder, as in Chicago and New York.

Bell of Minneapolis stated that confidence has been obtained by the correction of the objections and by the education of the undertakers. Accordingly, embalming schools have been established in connection with the state university where embalmers learn to prepare bodies on which autopsies have been done. Furthermore, the pathologists are careful to leave the vascular system suitable for embalming and refrain from making incisions on the body that show after it is dressed for burial. This cooperation has stimulated the undertakers to assist in gaining permissions for postmortem examinations.

Janeway cited other complaints by the undertakers, such as undue waiting for bodies, unkind treatment by attendants, undue mutilation by inexperienced men, delay in signing death certificates, etc. I am convinced that the example of Bell and Wooly may be followed profitably in Chicago. I am so deeply concerned about this subject that I feel we should take active steps toward improving the situation.

No systematic attempt has been made to educate the undertaker to an appreciation of the value of the necropsy to humanity. Some will not listen, of course, but ultimately they will react the same as those in other cities, with corresponding efforts on the part of the medical leaders. No attempt has been made to insure the undertaker against discrimination or collusion. Neither has any serious attempt been made to teach the embalming of bodies on which autopsies have been done. In fact there has been little in common between pathologists and undertakers, except enmity. Although our cause is altruistic and just, such may not be obvious to them, who are only business men. We must aid in every way possible to terminate a feud that has done and still is doing so much injury to science.

In recommending a solution of this problem, it seems to me that there is one course to pursue; that is, tactful publicity. Education will do more than any one thing. To improve the situation such education, to be effective, must be shown to benefit the physicians, public leaders, the general public and undertakers.

For the physicians there must be greater emphasis placed on the value of necropsies. There must be a greater effort and more dignity placed in this work by pathologists. In this way, pathologists will live down the popular impression that classes necropsies with anatomic dissection. Every physician should be taught to seek an anatomic instead of a clinical diagnosis on the death certificate. Physicians should be taught how to approach the relatives for a necropsy in a spirit that inspires respect and confidence. The approach must be sympathetic and business-like. The advantage for the sake of the family should be emphasized, as well as the benefit to science and the human race. They should be taught to give a simple report of the observations at necropsy to the relatives. Rokitsky's method of reconstruction of the medical history from postmortem observations would be entirely fitting.

In addition, plans should be started for the education of the masses. Such a campaign should include religious, social, professional and political leaders. Especially should efforts be made to change the antiquated laws by an appeal to the legislative bodies.

We should emphasize the value of postmortem examinations to our knowledge of medicine and the benefits derived from an enlightened medical profession. Health columns in the daily press, radio talks and special articles in the weekly and monthly journals may be tactfully and opportunely used. Efforts should be made to have an autopsy on every notable character, and the principal observations given publicity, so far as medical ethics permit. Finally, repeated attempts should be made to obtain the highly desirable cooperation of the undertaking profession.

THE PHYSIOLOGIC RÔLE OF COPPER. ARTHUR LOCKE and E. R. MAIN.

An analysis of the distribution of copper among the bacteria has indicated that the metal may be an essential constituent, concerned with the vital function of activating the organic molecules which take part in cellular respiration and synthesis.

VENTRAL SYMMETRIC HYPEROSTOSIS OF THE INNER TABLE OF THE CALVARIUM. LEROY W. YOLTON.

The complete report will be published in the ARCHIVES OF PATHOLOGY.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Oct. 24, 1929

HARRISON S. MARTLAND, *Presiding*

NEPHROSIS IN MULTIPLE MYELOMA. DAVID PERLA and LAWRENCE HUNTER
(by invitation).

Two instances of multiple myeloma with severe nephrosis with shrinkage of the kidney were reported. A review of the literature revealed several other similar instances. A study of the pathologic changes of the kidneys in instances of multiple myeloma associated with Bence-Jones albumosuria was made. From this analysis it was concluded that the pathologic changes found in the kidney of multiple myeloma consist of three distinct conditions, no one of which is constantly present, but all three of which may be present: (1) a nephrosis specifically associated in some way with the Bence-Jones albumosuria and the myeloma; (2) arteriosclerosis of the kidney, an independent vascular disease of the kidneys, present in a milder or severer form in almost every instance of multiple myeloma occurring in the age group of 50 to 70, and (3) calcium deposits in the kidney tubules, dependent on a destruction of bone and the release of large quantities of calcium into the blood.

Clinically, the nephrosis differs from the idiopathic type in the absence of edema and in the increase in the concentration of nonprotein nitrogen in the serum and an inability to concentrate urine with a consequently low specific gravity of the urine. Anatomically, the nephrosis is severe, and the kidneys contracted. The kidneys are small and pale, with a smooth surface and marked narrowing of the cortex and medulla with replacement by a dense cellular fibrous tissue. Though there is some hyalinization of a few glomeruli, this lesion is apparently associated with a concomitant arteriolosclerosis, the primary lesion being the destruction of the tubules.

DISCUSSION

PAUL KLEMPERER: The most interesting fact is that in these cases of chronic nephrosis there was no edema noted. It seems then that the conception that the degenerative change in the tubules is responsible for edema, is not true. It is interesting that these cases differ so markedly, not only clinically but also histologically, from the type of nephrosis which was held to be the most characteristic type of nephrosis, lipoid nephrosis. The more one studies such cases, the more one becomes convinced that the renal change is unimportant, and that the disease called

lipoid nephrosis has nothing to do with the kidney. I think the cases reported by Dr. Perla support such a conception.

NICHOLAS ALTER: What special staining methods have been used to determine the histologic nature of the degeneration?

HARRISON S. MARTLAND: In the first case reported, did I understand you to say that there were extraskelatal lesions in the spleen and liver?

DAVID PERLA: Yes, small foci.

HARRISON S. MARTLAND: Were they in the form of small, definite tumor formations, or just areas of myeloid metaplasia?

DAVID PERLA: They generally occurred in the capillaries.

HARRISON S. MARTLAND: I have had an idea that some forms of multiple myeloma, especially those in which the myeloblast and the erythroblast are the type cells, are closely related to panmyelosis. I have seen a single physical agent, viz., undue exposure to the x-rays and radium, produce several important diseases of the blood-forming organs, such as aregenerative leukopenic anemias, regenerative leukopenic anemias of the pernicious type, myeloblastic leukemias, lymphoblastic leukemias, osteogenic sarcoma of bones, radiation osteitis and panmyelosis, in one case so extensive as to mimic multiple myeloma, the flat bones of the skull being the seat of definite tumors of myeloid origin.

DAVID PERLA: In reply to Dr. Alter, no particular staining methods were used; we did try a great many strains recommended for the determination of the character of the protein substance in the tubules. I can give you the reference to the article which mentions the staining methods.

NICHOLAS ALTER: It would be important to differentiate it histologically from lipoid nephrosis.

DAVID PERLA: It seems to me the difference is obvious. In the ordinary lipoid nephrosis, you do not get the extreme contraction of the kidney. There were, however, fine lipoid droplets in the intact tubules.

ADENOMYOSIS OF THE URINARY BLADDER. DEMONSTRATION OF CONTINUITY BETWEEN A GLANDULAR DUCT AND A BLOOD VESSEL. ALFRED PLAUT.

A woman, 25 years old, without any relevant previous history, had suffered from dyspareunia and dysmenorrhea since her marriage one year before. On physical examination, adnexal adhesions were found. The other observations were unimportant. To his dismay, the surgeon at operation encountered a firm mass infiltrating the urinary bladder from behind. The pathologist consulted asked whether there had been urinary symptoms at the time of menstruation. After this was answered in the affirmative, he ventured a diagnosis of adenomyosis and suggested doing no radical operation, but excising only what could be taken without injury to the bladder. Rapid frozen section confirmed the diagnosis. The patient remained in good health.

Many specimens of adenomyosis in different organs, notably in the appendix vermiformis, have suggested to the author, as well as to others, the possibility and the high probability that glandular ducts might originate from lymph vessels or blood vessels. The literature contains a number of photomicrographs showing continuity between lymph spaces with low lining cells and glandular spaces with high cylindric epithelium. The fact, however, that epithelial cells may appear flattened, even without distention of the gland, and that endothelial cells may become high, makes it difficult to prove endothelial origin of epithelium to a skeptic. We consider ourselves fortunate, therefore, that this specimen of adenomyosis of the urinary bladder furnishes a series where a typical endometrium-like glandular duct is continuous with a blood vessel characterized by its elastic layers. (Demonstration of series.)

It is impossible to describe the series in a short abstract. The structure in question can be followed from the typical gland through stages in which the typical gland is surrounded by thick elastic layers to further stages in which

the lining is partly high cylindric and partly flat, like typical endometrium; finally to an ordinary blood vessel. Many glandular ducts in the slides have fragments of elastic tissue under the epithelium. It is the purpose of this paper to demonstrate the series for discussion. All theoretical considerations must be deferred.

DISCUSSION

PAUL KLEMPERER: I would not like to say that blood vessels and lymph vessels cannot develop glandlike structures. It is well known that one is sometimes startled by the presence of typical glandular structures lined with high endothelium in the pericardium in subacute or chronic inflammation. If Dr. Plaut thinks that some of the glandular structures in his series are definitely identical with blood vessels, it means that these glands have to be considered as of endothelial origin. In Dr. Plaut's series, one point struck me as peculiar. At the beginning of the series there was cytogenic tissue, and next to this the gland which he showed passing into a blood vessel. It seemed to me that the cytogenic tissue which we saw in the beginning of the series did not belong to this glandular structure, but to the adjacent one. I believe that there is a possibility that we are misinterpreting some apparently glandular structures when we consider them as mesodermal, that is, müllerian in origin, and not as mesenchymal, but I wonder if this is not an unusual occurrence. Or does the explanation which Dr. Plaut wishes to propose hold for the majority of the glandular structures in endometriosis?

LOUIS GROSS: I would like to ask whether Dr. Plaut attempted to make a wax model or some other reconstruction of this interesting specimen. I was struck by the same difficulty as was Dr. Klemperer, and that is, at one point in the series I was able to trace the apparent changes in the glandlike structure, and then there was an abrupt change into what appeared to be a blood vessel. Could it not be possible that we were coming to the end of the gland on one side, and found a knuckle of blood vessel on the other side? A wax-model reconstruction might be able to settle this question. Did you find any smooth muscle developing in this blood vessel, or what turned out to be blood vessel?

NICHOLAS M. ALTER: Endometriosis is always an embarrassing problem for the pathologists. I want to mention only some freakish cases. In one case, a young woman had hemorrhagic urination during menstruation. It could have been considered as a case of vicarious menstruation. Cystoscopic examination showed no ulceration of the bladder. When she came to the operating table, I had an opportunity to look into her abdomen as I was called for a frozen section. There was a nodule about 4 cm. in diameter over the convexity of the bladder posteriorly. Malignancy was thought of. It had to be resected with the mucosa of the bladder. In this nodule the histology of the glandular structures justified the diagnosis of so-called "endometriosis." In this particular case, the glands were traced per continuity from the nodule of the bladder wall through the adhesions to the uterus, which also showed diffuse adenomyositis. In another freak case, still more striking, a young woman had symptoms of appendicitis every month when she menstruated. Her appendix showed not only the usual microscopic picture of "endometriosis," but marked decidual changes of the stroma cells. In both these cases, the endometrial nature of these gland structures was demonstrated not only in the morphologic appearance, but also in the functional features. It would be out of place to discuss, here, whether these glands came from the uterine lining and how, or whether they differentiated to typical endometrial tissue from embryonic anlagen and came later also under the influence of ovarian action. I admit that preparations which Dr. Plaut produced with much care and labor, and which I studied but superficially, are strongly suggestive, but to me not convincing. There is no definite evidence that the glands and elastic tissue, although apparently intimately related, are of the same origin. As far as endothelial cells are concerned, metaplasia can change them to a higher type, but I would like to ask Dr. Plaut whether he found any ciliated cells.

ALFRED PLAUT: In reply to Dr. Gross, I hope we may make a wax model on a suitable case. I could not do it here because there was no more material.

Regarding Dr. Klemperer's question as to whether I consider all endometrioses subject to this explanation—certainly not. O. Frankl and his associates have proved the direct origin from the endometrium of certain endometrioses beyond any doubt. We have all seen the origin from the peritoneum beyond any doubt, and I hope that we will have a third origin of endometriosis, which I would like to call the interstitial. The relative frequency of these different origins has to be established. There is no reason why an unknown hormonal stimulus, probably ovarian, should not act on different elements in the same way. There is no reason why it should not stimulate the peritoneum and the endometrium and the mesenchymal cells, as well.

About the muscle tissue in the blood vessel walls, I would have to go over the slides again before I could answer that question.

The so-called glands in pericarditis I would not put in a direct parallel with the glands shown here; in my mind, they are vascular spaces with high endothelium. I do not believe that this comparison holds until we have seen the functional proof that these glands lined by high cells in the pericardium are really functioning secreting glands.

DR. ALTER said in one of his cases that bladder mucosa had to be resected. Adenomyosis invading the wall of the rectum or bladder practically always leaves the mucosa intact.

Reference to anlagen for an explanation, in my opinion, means we have no explanation. For instance, when the vaginal wall is completely full of glandular structures, and the trouble has developed at the age of 55, I do not see how a congenital anlage can have anything to do with it. It is the same with a diffuse endometriosis in the appendix and other organs.

I expected the series would be convincing to everybody, but I would like to ask how to explain the elastic lamellae around the gland. Even if we did not have the continuity with this blood vessel, how would one explain that a simple endometrium-like gland is surrounded by heavy layers of elastic tissue? I have seen many thousands of slides from adenomyosis, and so far I have not seen such heavy elastic layers. I am going to stain all slides of adenomyosis with Weigert's, and report to you next year or in two years what I find.

ACUTE HEMOLYTIC ANEMIA. THREE ADDITIONAL CASES WITH A REVIEW OF THE LITERATURE. MAX LEDERER.

In 1925, in the *American Journal of Medical Sciences* (170:500, 1925), the author published a description of three cases of an undescribed form of acute hemolytic anemia. These cases presented a clinical picture of anemia which developed within a few days and progressed at an alarming rate. In the present communication, a study of three additional cases observed by the author is reported, with a résumé of the literature including three others mentioned by various authors. All six cases presented similar clinical and hematologic pictures, with certain variations. The age incidence was from 6 months to 35 years. Five were in males and one in a female. The history of onset in three cases was three days; in two, six days, and in one, two days. The onset in all six was characterized by the rapid development of pallor, icterus, weakness and rise of temperature. In four there was vomiting, in one diarrhea, in one backache, in one headache and in two hemoglobinuria. On physical examination, six showed pallor and icterus and five fever, while in four there was noted splenic enlargement, and in three hepatic enlargement. The classic evidences of hemolysis were demonstrable in all. The blood showed in all cases a severe anemia, the red cell count falling in one case to 760,000 per cubic millimeter; the stained preparation in all cases showed the presence of varying numbers of megaloblasts and erythroblasts and myeloblasts. All the patients promptly recovered after a transfusion of unmodified blood, the nucleated red cells disappearing within twenty-four hours and the hemoglobin and red cell count increasing rapidly, in some instances

up to more than three times. Restudy of the patients several years after recovery showed no sequelae in any instance.

DISCUSSION

CHARLES NORRIS: I would like to ask if a seasonal occurrence has been observed, and if the cases were all in Brooklyn, and if they were, did they all come from the same district?

ELI MOSCHCOWITZ: I think Dr. Lederer is lucky to have seen all these cases. I have kept my eyes open for other cases, but have not had the occasion to see another since my last report. There is no doubt that the case which I reported seemed like those of Dr. Lederer, except that in his cases the patients all recovered. It is true that the examinations of the blood in my case were not as carefully done as in Dr. Lederer's cases. My case occurred in a child with a rapidly increasing anemia, which was accompanied by a high color index; as in Dr. Lederer's cases a transfusion was done, but the patient did not recover. At autopsy, I found hyaline thrombi in the peripheral arterioles and in the capillaries. Obviously, the six cases which Dr. Lederer reports represent nothing more than a clinical syndrome thus far. In order to complete his study and to make this a definite disease, a precise pathologic study is still necessary.

FREDERICK H. DIETRICH: Have all these cases the same racial background?

LOUIS GROSS: The striking increase in red blood cells within forty-eight hours makes one wonder whether increased blood concentration at this period may not be at least a factor. Did you make any studies of the blood volume during this remarkably sudden increase in red blood cells?

ALFRED PLAUT: I want to ask two purely technical questions. I would like to ask how a hemoglobin of 14 is read. With the Sahli instrument, I am unable to make a reading below 30. My second pedantic technical point is why does everybody, including Dr. Lederer, report the number of nucleated red cells in relation to the leukocytes. In my opinion, they have nothing to do with each other, and I always give the number of nucleated cells in relation to the number of red cells, which in my opinion is the more logical way. I would like to know whether any such case is on record which has become chronic. I had the opportunity of seeing a patient who for twenty years has had a hemoglobin around 40, and 5 per cent nucleated red cells, without being very sick.

H. S. MARTLAND: Could the chronic, more or less benign cases be confused with von Jaksch's anemia or the erythroblastic anemias of infancy? Are the acute cases essentially cases of hemolytic anemia due to increased activity of the reticulo-endothelial system, or have you formed any opinion as to their etiology?

MAX LEDERER: Regarding Dr. Martland's question, in 1925 Dr. Klemperer, in a personal communication, suggested as an explanation that the exciting agent of the disease exercised a selective action on the reticulo-endothelial system as a whole, affecting its productive, as well as its destructive, function; that the erythroblastosis is accounted for by the stimulation of the productive function and the hemolytic anemia by the stimulation of the destructive components and that the destruction continues at a greater rate than the production.

H. S. MARTLAND: Were there many immature leukocytes in the circulating blood?

MAX LEDERER: Regarding the leukocytes, the myeloid tissues are stimulated causing an increased production of leukocytes with the appearance of small numbers of immature forms. The high degree of leukocytosis is probably due to this excessive production, and since the reticulo-endothelial system does not concern itself with the destruction of leukocytes, they heap up in great numbers.

As far as seasonal incidence is concerned, the cases occurred at all times of the year. They were not confined to Brooklyn. One case occurred in the mountains after a vacation to increase hemoglobin. There were two cases reported in Denmark, one in France and one in Missouri.

As far as race is concerned, two cases were in Danes and two cases, which are going to be reported by Dr. Lazarus, were in negroes.

In regard to blood volume, we have not done any studies on blood volume. The general appearance of the patients following transfusion, and their remarkable improvement showed a profound increase in the number of blood cells. The hemolysis due to the destruction of red cells was manifested in the tremendous hemoglobinuria.

I agree with Dr. Plaut regarding the reading of a hemoglobin of 14; that is more or less arbitrary. We use the Dare hemoglobinometer exclusively, and our Dare is thoroughly checked by the Newcomer, so we are certain that the readings on the Dare are close to those obtained on the Newcomer. The only reason for reporting erythroblasts in terms of the number of leukocytes per hundred cubic centimeters is because erythroblasts are counted at the same time the differential count is done, and it is a habit we have fallen into. I do not suppose anybody has had the courage to report them in absolute numbers, as most of us do not report the differential white cells in absolute numbers. The studies had to be done quickly, and the blood specimens obtained were examined quickly, so we feel that the figures, as we gave them for practical purposes, emphasized the diagnostic point as well as would an absolute count.

BALANTIDIUM COLI ENTERITIS: REPORT OF A CASE OBSERVED IN NEW YORK CITY. HERBERT LAMPERT (by invitation).

This case of balantidial colitis occurred in a 60 year old Porto Rican woman who died from pneumonia. The lesions, which were found at autopsy, were limited to the entire length of the colon. The ulcerations resembled those of amebic dysentery. It was noted that the more recent ulcerations were located at the proximal portion of the colon, while the more chronic lesions were situated more distally.

In attempting to study the manner in which the balantidia invaded the mucosa, serial sections were cut and examined, of what was apparently normal mucosa. Sections were shown in which the balantidia were seen within the crypts of the colon, which were distended with an exudate of polymorphonuclear leukocytes and debris. Other sections showed the gradual erosion of the mucosal gland with extension along the lymphatics to other portions of the colon. All the ulcerations showed secondary bacterial invasion. Many of the balantidia were found within large blood vessels. In spite of the latter observation, there were no lesions found in either the liver or the lungs, although such observations have been reported by other investigators.

DISCUSSION

PAUL KLEMPERER: In view of the increasing Porto Rican population, I think it is important to emphasize that we can expect to find such and similar cases.

FIBROSARCOMA OF THE PLEURA IN ITS RELATION TO ENDOTHELIOMA. G. V. RABIN (by invitation).

The paper refers to the diffuse type of pleural tumors which completely ensheath the lung. There have been about eighty cases reported under various headings as carcinoma, endothelioma and sarcoma. The endotheliomas are considered as arising from either the serous lining cells or the cells of the subpleural lymphatics. In the latter cases, however, the growths appear rather to be extensions to the pleural lymphatics from primary pulmonary tumors.

A case was presented of a diffuse pleural neoplasm which showed both epithelial and mesenchymal characteristics. The patient, a girl, 18 years of age, was admitted with a history of pain in the left side of the chest for eighteen months. On physical examination, the left side of the chest was found to bulge forward markedly. The percussion note was flat. The roentgenogram showed a diffuse shadow over the entire left side of the chest with marked displacement of the heart to the right. On pleural puncture, the needle met with great

resistance. No fluid was withdrawn, but a particle of tissue removed with the needle showed histologically a picture that resembled a spindle cell sarcoma.

The patient died shortly thereafter. At autopsy, the left lung was found collapsed and completely ensheathed by a thick nodular neoplasm which infiltrated the chest wall. Histologic examination showed the tumor to be made up of cells, distinctly epithelial, with large pale nuclei containing nucleoli and a sharp nuclear membrane. The cytoplasm was abundant. There were many giant cells. There were, however, intercellular fibers which stained black with Bielschowsky, blue with Mallory fuchsin aniline blue, brown with the phosphotungstic hematoxylin and red with the van Gieson stain. These fibers were delicate and completely surrounded each cell in most portions of the specimen.

Records of three similar types of pleural tumors were discovered in a study of the literature of sarcoma of the pleura. In each case, the cells presented typically epithelial characteristics. In order to explain this histologic picture, the characteristics of the mesothelial cell, the cells lining the pleura, were discussed. Genetically, they are derived from the celomic epithelium, which is closely related to the mesenchyme. Under experimental conditions, their fibroblastic potentialities, indicated from their embryologic origin, have been proved, both in tissue cultures and in inflammatory reaction of the pleura and peritoneum. Since the mesothelial cells that line the pleural cavity are possessed of both epithelial and fibroblastic potentialities, it is concluded that the entire group of diffuse pleural neoplasms has a common origin in the mesothelium and should be considered under the one single heading of mesothelioma.

DISCUSSION

ALFRED PLAUT: I fully agree with Dr. Rabin. I would like to know whether intercellular bridges have been sought for. They are found frequently, if one looks for them, in structures arising from the peritoneum. As some of you will remember, several years ago I had the opportunity of reporting on peritoneal cysts here. The observation of the epithelial character of the lining cells of the peritoneum is a matter of daily routine to the man who does gynecologic pathologic investigation. In every tubal gestation I find high peritoneal cells. In every fifth normal tube, I find typical squamous epithelium in the serosa. In the last meeting of the German Pathological Society, Hamdi reported epithelial tumors of the pericardium. He called them celothelioma, which is better than mesothelioma, because the term "meso-" is used for many different things.

A. M. SALA: The title of Dr. Rabin's paper as given in the program led me to bring up this specimen of what I have tentatively diagnosed as fibrosarcoma. It was removed at operation just a few days ago from a woman's right pleural cavity, where it seemed to spring from the diaphragmatic pleura. It weighs 1,675 Gm. Because this is an entirely different tumor from the one considered by Dr. Rabin, I shall make it the subject of a detailed presentation before the society in the near future.

C. B. RABIN (closing the discussion): I am glad to see that specimen. It belongs to the other type, not the diffuse type of tumors, and it is only the diffuse type that I am discussing. The latter are the ones which I believe should not be called fibrosarcoma, but one should realize their point of origin. Sarcomas similar to the one of Dr. Sala were collected and described by Schneider. They form an interesting group. However, they have no relationship to the type under discussion. They arise from the subpleural connective tissue.

In reply to Dr. Plaut's question about intercellular bridges, we saw none.

STUDIES IN THE CHEMISTRY AND CYTOLOGY OF SPINAL FLUID AFTER THE INJECTION OF PROCAINE HYDROCHLORIDE FOR SPINAL ANESTHESIA. ALFRED H. IASON and MORRIS STEINER (by invitation).

In a great majority of cases, it has been shown that spinal anesthesia is less toxic and produces less ill after-effects than general anesthesia. However, cases have been cited by Munchmeyer, Madden, Gabbett, Berand, Hatcher and Eggleston

in which fatalities resulted following the use of this type of anesthesia. In addition, many cases manifested such untoward results as headache, retching, vomiting and paresthesias of the leg. It was thought that if some of these sequelae were due to toxic and irritating actions of the medicament employed, some changes in the spinal fluid must have resulted. It was with this in mind that the following investigation was undertaken.

The spinal fluid of thirty-one patients was examined before and twelve hours after the injection of procaine hydrochloride into the canal. The cytology and chemistry, which included the nitric acid ring test for albumin, the Noguchi test for globulin, Fehling's test for reducing substance, the colloidal gold reaction and finally a quantitative determination of sugar by the Folin-Wu method, were studied.

Of the thirty-one spinal fluids, only fourteen permitted accurate cytologic studies; all the others contained from few to many red blood cells, which were considered as due to trauma incidental to the lumbar tap. Of these 14, 11 showed a definite pleocytosis varying from 800 cells, all of the polymorphonuclear variety, to 20 cells, all lymphocytes. Two showed a slight pleocytosis—12 cells, all lymphocytes; one, a normal count—5 cells, all lymphocytes.

In twenty of the thirty-one cases, the quantitative determinations of sugar were studied. In all twenty cases there was an increase in the postoperative specimens varying from 7 to 135.2 per cent. In but three cases could the increase be considered within normal limits, being less than 10 per cent. The average rise calculated on the basis of percentage increase for each case was 37.3 per cent. Just what the significance of this increase in sugar is, cannot be stated. Further studies are being made in which simultaneous blood and spinal fluid sugar determinations are being done, before and after the injection of procaine hydrochloride, in order to observe whether or not any relationship exists between the sugar content of the blood and that of the spinal fluid under these conditions.

The addition of procaine hydrochloride to spinal fluid *in vitro* does not cause any increase in the reducing substance.

The albumin was not increased nor was globulin present in any of the cases. The colloidal gold was not reduced in any case, which indicates that the protein content of the spinal fluid was not altered after the injection of procaine hydrochloride for spinal anesthesia.

DISCUSSION

ALFRED H. IASON: In selecting cases, we were careful to use a variety, i. e., carcinoma of breast, appendicitis, hernia and fibromyomata uteri. The age of the patients varied from 11 to 69 years. There were nine males and twenty-two females. In the oldest patient, a woman of 69, with an incarcerated hernia, the blood pressure dropped from 100 to 80, systolic, and 80 to 60, diastolic. The largest fall in systolic blood pressure was 74, and that in diastolic pressure was 42, with 10 as the lowest fall. We watched the patients for postoperative complications. Seventy-five per cent of them had to be catheterized for the first three days; six patients vomited for one day; three vomited or retched at the time of operation; two complained of pain in the right leg for two days; one complained of headache and dizziness. We also noted that in subsequent lumbar taps the rate of flow was moderately increased in 30 per cent of the cases. In children under 14 years of age, and in adults in whom the operative procedure was limited to the lower part of the abdomen, I usually found that from 75 to 125 mg., instead of a whole ampule of 200 mg., was sufficient. I also observed that when giving less than the full ampule of procaine hydrochloride a complete anesthesia was late in appearing, but there was an absence in a large degree of such operative sequelae as vomiting, urinary retention and vertigo. With a smaller amount of anesthesia, there followed an elimination of postoperative sequelae as mentioned. In a series of about a thousand cases, only one case of postoperative pneumonia occurred, which probably had no relation to the anesthesia.

FREDERIC FELDMAN (by invitation): Did you use ephedrine?

ALFRED H. IASON: We used it routinely, in children using half an ampule. We also used procaine hydrochloride without the injection of epinephrine hydro-

chloride subcutaneously to anesthetize the skin before inserting the needle into the spinal canal. I always punctured the third interspace, whether in adults or children. I reported on one adult on whom I did a radical mastectomy for carcinoma of the breast under spinal anesthesia in whom I utilized the third lumbar interspace, and when the operation was finished, I had anesthesia as far cephalad as the mastoid bone.

FREDERIC FELDMAN: Do you think the rise in sugar could be due to the ephedrine?

PAUL KLEMPERER: There are a few cases on record in which after spinal anesthesia an aseptic meningitis occurred; in all these cases the patients recovered.

ALFRED H. IASON: At the Jewish Hospital, we have not had any mortality from spinal anesthesia. In addition, I might add that a mild cardiac condition is not a contraindication to spinal anesthesia.

DIVERTICULA OF THE COLON. ROBERT P. WALLACE.

Diverticula of the colon have long been noted, but it was not until 1849 that Cruveilhier first described them in some detail. Diverticulitis was first recorded and the name added to the condition by Habershorn in 1857. It was not till 1898 that diverticula were recognized as being of much importance, when Glazier pointed this out and stressed the frequency with which they are present. The first really exhaustive paper appeared in 1904 by Beer, and three years later Moynihan's classic paper gave a differentiation from cancer and stressed its surgical importance.

Later years, with the increased frequency and accuracy of diagnosis by means of the roentgenogram it was found that diverticula were the basis for many indefinite "colon complaints" and that the complications requiring surgical intervention were comparatively few. Chief among the present day investigators are Robertson, Case, Mailer, Patterson, Spriggs and Marxer.

Statistics from the Mayo Clinic showed records of 1,918 cases of diverticulosis. At autopsy, Robertson found that 5 per cent of the people past 40 years of age had diverticula of the colon. Also at autopsy, Mailer found 7 per cent of the adults had colonic diverticula. These observations fairly well approximate the results of roentgen examination; for in 26,700 cases of gastro-intestinal disease 5.9 per cent were associated with diverticula. On the other hand, Spriggs and Marxer in England found in 1,000 consecutive cases 10 per cent with colonic and 1 per cent with small intestinal diverticula. They also state that half the demonstrated diverticula gave symptoms after observation over a number of years and the other half were silent. These are the highest figures that I have been able to find.

Diverticula formerly were described as being of congenital and acquired origin. The congenital type consisted of all coatings of the intestine, while the acquired type represented herniations of the mucosa and submucosa through the muscle wall. This classification is still mentioned now, but it is the trend of thought that most of the colonic diverticula are acquired, and it is doubted whether or not congenital pocketings occur in this location.

Diverticula of the duodenum, on the other hand, are probably for the most part congenital and differ materially from the others in that they contain the whole intestinal coating, have wide openings, are shallow and frequently contain gastric mucosa or pancreatic tissue at their tips. This belief was given further credence when Dr. Thyng demonstrated such diverticula of the duodenum in the embryo.

The prediverticular state, that is, before sacculation has occurred, was described in 1925 by Marxer. His description was based on x-ray evidence, and when subsequent films were made several years later actual sacculation was demonstrated in such areas. Surgical specimens of such a stage, when examined microscopically, reveal that this portion of the intestine is inflamed and there is a thinning out of the musculature. This was observed by Glazier, Patterson and Wilson.

In the colon, diverticula occur in any portion of the circumference of the intestine, but most usually on the antimesenteric border where the blood vessels and lymphatics enter. In the small intestine, however, they occur between the layers of the mesentery. In the large intestine, the sacs are usually numerous and small, and have small openings, while in the small intestine the sacs become much larger.

Pathologic Changes in Diverticula.—In serial x-ray pictures, it has been shown that diverticula contract, as peristaltic waves progress through the gut, in an effort to expel the contents. However, as the sac becomes larger, the muscle fibers disappear, the contents stagnate and become hardened. This stercolith by pressure and irritation excites inflammation. This starts first at the neck and opening of the sac and spreads into the sac and onto the wall of the colon. This area is not often the site of ulceration, but fibroblasts invade it, and scar tissue is formed. As this contracts, the opening is widened, the depth of the sac is diminished and the contents are gradually evacuated. This is another example of the remarkable reparative process that occurs in the body following injury.

DISCUSSION

CHARLES T. OLCOTT: There were twenty or thirty diverticula in the first portion of the jejunum in the patient, a specimen of which I brought to exhibit. The patient was a man of 71 who died of a perforated gastric ulcer. He also had a diverticulum of the duodenum. The diverticula were an accidental observation at autopsy.

BORIS KWARTIN: I should like to ask if all these cases were postmortem or operative cases. In one case of a neurotic young man about 21 years old who complained of gastro-intestinal symptoms of a vague character, a series of x-ray pictures was taken, and a permanent defect was found in the postpyloric region; on account of the x-ray evidence, rather than the symptoms, an operation was performed. When I received the specimen, I could not demonstrate an ulcer, but I did not find a little diverticulum, 2 by 2.5 cm. All the coats were completely intact. It was covered by mucosa and there were no signs of inflammation or other pathologic change.

PAUL KLEMPERER: These juxtapyloric diverticula are not so rare; I find them rather frequently. An interesting case was that of a diverticulum near the papilla of Vater, pressing on the common duct. In this case, the main symptom of the patient was jaundice, for which an operation had been performed and it was apparently due to the pressure of the diverticulum on the common duct.

ROBERT P. WALLACE: These were all observed at autopsies, and they have become so frequent that they are not a rarity any more.

Book Reviews

THE LIFE OF HERMANN M. BIGGS, M.D., D.Sc., LL.D., PHYSICIAN AND STATESMAN OF THE PUBLIC HEALTH. By C.-E. A. WINSLOW, Dr. P. H., Professor of Public Health, Yale School of Medicine; Member, Health Committee, League of Nations, Geneva; Member, Public Health Council, State of Connecticut; Past President, Society of American Bacteriologists and American Public Health Association. Cloth. Price, \$5, net. Pp. 432, with illustrations. Philadelphia: Lea & Febiger.

Here is an interesting biography of a physician who began his medical career as a pathologist and became one of the great leaders of the world in public health. Hermann Michael Biggs (1859-1923) was graduated from Bellevue Medical College in 1883 and served as intern in Bellevue Hospital. Many years later he commented on this period as follows: "It seems strange often in looking back after half a life-time, over the passage of many years, what apparently insignificant incidents have determined largely the course of one's life. How clearly now I recall the incident which first directed my thoughts to bacteriology and tuberculosis. I was in my last year of medical school. Our beloved friend, Dr. Welch, was Professor of Pathology at Bellevue and was conducting a private class in normal and pathological histology. I was a member of one of those classes, just after the publication of Koch's classical work on the Etiology of Tuberculosis. In his most lucid and fascinating manner he told us of this great work and its significance to the future development of medicine. He showed us methods of staining sputum and demonstrated tubercle bacilli. I can see now quite clearly the steam rising from the dish of Carbol-fuchsin in the sand-bath containing sputum, while he talked. This served as my first inspiration. . . ." The book is rich in choice illuminating glimpses like this. It is worthy of note that Biggs' first teacher in pathology now writes with comprehensive grasp the introduction to this biography of his pupil. When Biggs returned from Germany in 1885 he was appointed one of the instructors in the Carnegie Laboratory, then just opened, and gave instruction in bacteriology. He also came early into close relations with that other great pioneer American pathologist, T. Mitchell Prudden, whom he spoke of as his "silent but influential partner" and who played a highly significant part in the development, in intimate association with Biggs, of the work of the Health Department in New York City. One meets these two pathologists again and again in the book. Biggs also practiced medicine and was a trusted physician and excellent consultant. He was successively teacher of pathology, of therapeutics and of medicine, and during his earlier professional years he published papers on pathologic subjects. He was president of the New York Pathological Society in 1891. These facts are cited not merely to show that Biggs entered on his great life-work by the gateway of pathology, but also to make it clear that his biographer incidentally throws vivid sidelights on the early history of pathology in this country.

Shortly after Biggs became connected with the Carnegie Laboratory he was sent to Plymouth, Pa., to study the famous outbreak there of typhoid fever, but it was not until 1887 that he began to do work for the New York City Health Department. The occasion was the danger of the introduction of cholera, and he then suggested the advisability of establishing in the department a division of bacteriology and disinfection. This is the beginning of his work in public health on which his permanent fame so securely rests. The achievements credited to him in this field are monumental. His four major contributions to public health administration while in the service of the city of New York are listed as follows by his biographer: Establishment of the first municipal diagnostic and research public health laboratory; the administrative control of diphtheria

and the administrative introduction of diphtheria antitoxin; the administrative control of tuberculosis, and the program for the protection of child health. Biggs severed his connection of more than twenty-six years with the city health department at the beginning of 1914 to become State Health Commissioner, finally accepting the position after much persuasion. Previously he had been chairman of a commission that had prepared a new, recently enacted state public health law, which included important reforms. In the conduct of the state office "he demonstrated concrete administrative procedures which have formed the models for all subsequent progress in the difficult art of community health organization." The circumstantial story of the life of this man who modernized public health administration in accord with the newer knowledge of infection and in other fields as told in this book is of unusual interest. The rich materials are handled with great skill and competence. The style is clear and fluent. Biggs is fortunate in his biographer. Incidentally, there is traced at the same time the development of modern public health administration as necessary to provide the proper background for understanding the significance of Biggs' work. Many figures—scientists, teachers, administrators, politicians—move across the pages and help to tell how a quiet, rather silent man, with a frail constitution, rose to "a position almost unique in public confidence and influence in matters concerned with health and control of disease." The illustrations, mostly portraits, add to the interest. The publisher has done his part well. The book is an important and attractive addition to the biographic literature and is an outstanding medical biography.

THE FEMALE SEX HORMONE. By ROBERT T. FRANK, M.D., Gynecologist to Mt. Sinai Hospital. Price, \$5.50. Pp. 324, with 86 illustrations and 36 graphs. Springfield, Ill.: Charles C. Thomas, 1929.

This elaborate monograph concerning the female sex hormone, in the field of which the author has done so much work of fundamental importance, is divided into two main parts. The first part deals first with anatomic and physiologic matters of basic significance and then with the results of the investigations of the female sex hormone, its actions, sources and chemical nature. The presentation is minute and detailed, so much so as to be almost confusing at times, but it gives a reliable and complete summary of the literature in question. For this reason the book will be a helpful guide to sources for other workers. At the end of part I is a list of 491 complete references. The second part presents the results of clinical investigations by the author on the basis of "the female sex hormone blood test." The technic of the test and the results of its application under various conditions, the physiologic actions of the hormone on women and the treatment for functional diseases of the female reproductive organs are described in detail. At the end is a further list of references, numbers 491A-518, and as the previous list is referred to frequently in this part, it seems that the two lists of references might have been consolidated with advantage into one list at the end. In view of the great many details, frequently repetitious, in both parts I and II, it is of great value that the last chapter gives a clear and connected statement in summary and review. There is complete both subject and author index. The book is an earnest, able and successful effort to picture the present state of our knowledge of the female sex hormone. The rapid progress is impressive and the outlook promising.

GREEK MEDICINE, BEING EXTRACTS ILLUSTRATIVE OF MEDICAL WRITERS FROM HIPPOCRATES TO GALEN. Translated and annotated by ARTHUR J. BROCK, M.D. (Edinburgh), translator and commentator of Galen. Price, \$1.75. Pp. 256. New York: E. P. Dutton & Company.

The translator writes an instructive and interesting introduction on Greek medicine and its development, with Hippocrates, his teachings and Galen as the main topics. One commonly speaks of Hippocrates and Galen as practically

contemporaneous, but they are separated by six hundred years, and Galen always includes Hippocrates among "the Ancients." Many persons will be surprised to learn how much is known about Galen himself, mainly from autobiographic glimpses in his medical writings. In commenting on certain ancient theories, Dr. Brock makes the startling statement (page 17) that "if the doctrine of Erasistratus shows certain parallels with Osteopathy, that of Asclepiades reminds us of yet another modern medical system, also of American origin, namely, the so-called 'Electronic Reaction of Abrams.' . . . As Asclepiades employed the then new atomic theory in explaining vital processes, similarly Dr. Albert Abrams of San Francisco (1863-1924) did with the modern theory of electrons." Dr. Brock's knowledge of Abrams' claims and their nature is sadly defective. The main part of the book is made up of translations with introductory annotations of extracts from Hippocrates and Galen. There are translations also of short extracts from Plato, Aristotle, Rufus of Ephesus, Diodorus and Aetius. All the extracts included, except those from Aristotle, have been translated by Dr. Brock directly from the Greek. There is a helpful index. The book is a capital introduction to Greek medicine. The first Hippocratic aphorism, as translated in this book, follows: "Life is short, the Art long, occasion sudden, experience fallible, and judgment difficult. Not only must the physician show himself prepared to do what is needed, he must make the patient, the attendants, and the surrounding circumstances cooperate with him."

KLINISCHE LABORATORIUMSTECHNIK. HERAUSGEGEBEN VON PROF. DR. THEODOR BRUGSCH und PROF. DR. ALFRED SCHITTENHEIM. Zweite, Vollständig neu bearbeitete Auflage der "Technik der Speziellen Klinischen Untersuchungsmethoden." Volume 4. Paper. Price, 50 marks. Pp. 2101-2840, with 328 illustrations and 8 colored plates. Berlin and Vienna: Urban & Schwarzenberg, 1929.

This volume contains technical and critical descriptions of the biologic diagnosis of pregnancy by H. Runge, skin function tests by Schwenkenbecher and Moog, diagnosis of the nervous system by H. Lewy, psychologic methods, with especial regard to vocational tests, by A. Moll, psychiatric methods by Birnbaum, esophagoscopy by W. Wolff, gastroscopy by H. Elsner, proctosigmoidoscopy by H. Strauss, thoracoscopy by Jakobalus, tracheobronchoscopy and laryngoscopy by W. Frühwald, rhinoscopy by J. Schnierer, examination of the acoustic apparatus and of the labyrinth by O. Benesi, examination of the accessory nasal cavities by J. Fischer, cystoscopy by Rumpel and ophthalmoscopy by W. Meisner.

The editors make the comment that all these methods have developed in such close contact with internal medicine that they have become part of it. They admit that the title of the work has become too narrow for its contents and would now prefer to call it "Working Methods of Scientific Medicine." It seems, however, like a wasteful duplication of effort to attempt to bring into one book so many methods which require special technical training and which are better dealt with in monographs. No conscientious internist will attempt to perform gastroscopy without special study and technical training, and some will not have it done even by experts. Superfluous as many chapters seem they are nevertheless interesting to read and may increase the general information of the specialist. An abundance of references to German literature and an index of 47 pages are of course valuable assets of the work.

Books Received

THE ADRENALS, THEIR PHYSIOLOGY, PATHOLOGY AND DISEASES. By Max A. Goldzieher, M.D., former Professor of Pathology, University of Budapest; Director of Laboratories, United Israel Zion Hospital, Brooklyn, N. Y. Price, \$7.50. Pp. 436. New York: The Macmillan Company, 1929.

THE MEDICAL MUSEUM, MODERN DEVELOPMENTS, ORGANIZATION AND TECHNICAL METHODS BASED ON A NEW SYSTEM OF VISUAL TEACHING. By S. H. Daukes, O.B.E., M.D., D.P.H., D.T.M. & H., Director of the Wellcome Museum of Medical Sciences affiliated to the Bureau of Scientific Research. Pp. 172, with 44 illustrations. London: The Wellcome Foundation Ltd., 1929.

METHODS AND PROBLEMS OF MEDICAL EDUCATION. Fifteenth Series. Pp. 76. New York: Rockefeller Foundation, 1929.

This number contains a complete description of the Albany Medical College, Union University, Albany, N. Y.

INSECTS, TICKS, MITES AND VENOMOUS ANIMALS OF MEDICAL AND VETERINARY IMPORTANCE. By Walter Scott Patton, M.B., Ch.B. (Edin.), F.E.S., Dutton Memorial Professor of Entomology, Liverpool University and Liverpool School of Tropical Medicine, and Alwen M. Evans, D.Sc., Lecturer on Entomology, Liverpool School of Tropical Medicine. Part 1. Medical. Pp. 785, with 374 illustrations, 60 color plates, 3 maps and a large illustrated revision sheet. Price, 20 shillings, postpaid. Liverpool: School of Tropical Medicine, 1929.

THE HEALTH OF WORKERS IN DUSTY TRADES: II. EXPOSURE TO SILICEOUS DUST (GRANITE INDUSTRY). By A. E. Russell, Past Assistant Surgeon, R. H. Britten, Associate Statistician, L. R. Thompson, Surgeon, J. J. Bloomfield, Assistant Chemical Engineer, U. S. Public Health Service (with sections on autopsy material by Dr. L. U. Gardner, and on silica by Prof. A. Knopf). United States Public Health Service Bulletin 187, July, 1929. Price, \$1.15. Pp. 206. Washington, D. C.: U. S. Government Printing Office, 1929.

CONTRIBUTIONS FROM THE LABORATORY AND MUSEUM OF COMPARATIVE PATHOLOGY OF THE ZOOLOGICAL SOCIETY OF PHILADELPHIA, 1922-1929. Philadelphia: Zoological Society, 1929.

BACTERIOLOGY, ESPECIALLY DETERMINATIVE BACTERIOLOGY. By Prof. Dr. K. B. Lehmann of Würzburg and Prof. Dr. R. O. Neumann of Hamburg. Seventh edition. Volume 1A, parts A and B. Technique and General Determinative Bacteriology. Translated by Dr. Robert S. Breed, Chief in Research, New York Agricultural Experiment Station, Geneva, N. Y. Pp. 103, with 5 colored plates. New York: G. E. Stechert & Company (Alfred Hafner), 1930.

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The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients

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CONTENTS

- I. General Correlations in 100 So-Called Normal Men
- II. The Clinical Status of the Group of 100 "Normal" Men
- III. Detailed Study of the "Normal" Group and of Miscellaneous Clinical Patients
 - Method of Presentation of Results
 - Blister Time
 - Capillary Permeability
 - Inflammatory Index
 - Calcium, Potassium and K/Ca Ratio
 - Total Proteins
 - Globulins
 - Kromayer Erythema Time
 - Basal Metabolic Rate
 - Resistance of the Skin to Electric Current
 - Muscle Reactivity
 - Reaction of Pulse Pressure to Epinephrine
 - CO₂ Combining Power
 - Ice Reaction Time
 - Weight/Length Ratios
 - Cholesterol
 - Reactivity to Epinephrine: The Wheal
 - Reactivity to Epinephrine: The Flare
 - Reactivity to Thyroxin: The Wheal
 - Reactivity to Thyroxin: The Flare
- IV. The Patient with Exophthalmos and the Nervous Patient
- V. Patients with Glaucoma and Their Vascular Reactions
- VI. Sensitized Persons and Persons with Diseases of the Skin
- VII. A Study of 83 Tuberculous Patients
 - A. General Correlations
 - B. Detailed Study of the Reactions of Persons with Tuberculosis
 - C. Clinical Study of Alterations in the Permeability of the Capillaries in Patients with Tuberculosis
- VIII. The Intracutaneous Reactions to Injection of Pharmacologic Substances During Chill and Fever
- IX. Discussion and Conclusions

I. GENERAL CORRELATIONS IN ONE HUNDRED SO-CALLED NORMAL MEN *

The studies in which during the past five years, one of us (W. F. P.) has been interested had their inception in the problems of nonspecific resistance to disease. Closely associated has been a consideration both of allergy and of autonomic derangement, during the course of which individuals react in an abnormal manner to a nonspecific stimulus.

The clinical picture of disease is obviously the reaction of the individual organ or the organism as a whole to an insult. Normally, the insult provokes stimulation, made manifest in various ways, but cellular inhibition, fatigue, paralysis and death may all play a part simultaneously in the sum total of this clinical picture. Not only does the insult vary qualitatively as it may quantitatively, but the individual response will be modified because of inherent differences in the inherited germ plasm, because of differences in the relative activity or inactivity of the glands of internal secretion, because of diet, age, fatigue, previous experience (sensitization or immunity), preexisting or concomitant disease, psychic states, climate, temperature, etc.

It is a subject that does not lend itself readily to study because the degrees of reactivity of the different tissues of the body which we commonly use for examination (skin, nervous tissues, mesenchyme [bone-marrow, leukocytes, endothelium, etc.]) are not necessarily coordinate. Certainly, the reactivity of the epithelium may not correspond with that of the smooth musculature of the blood vessels, and the smooth musculature of the blood vessels may give no index of the status of the capillary endothelium. Recent investigations of the autonomic responses of the body have made this clear.

In its broader aspects, such a study deals with individual constitutional reactivity. But we have felt that in seeking to define constitution in terms of measurable biologic reactions rather than in developmental attributes, some progress might be achieved. The clinician speaks of "lowered resistance" or "good resistance." Generally that is an estimate based on the appearance of the patient, the color and the texture of the skin, the muscular development, the posture and the tonus, the appearance of the fat depots and of the mucous membranes and the mental attitude—the many subtle differences in the physical appearance of the patient. In making his general estimate, the physician usually fuses both constitutional factors and the factors that are the result of environmental forces (condition).

* From the Department of Pathology of the University of Illinois College of Medicine.

To Eppinger and Hess¹ we owe the introduction of one of the first of the modern methods useful in the estimation of individual reactivity, namely, the injection of epinephrine hydrochloride. Eppinger and Hess classified their patients as sympathicotonic or vagotonic. Clinical experience, however, has clearly demonstrated that this sharp division is not tenable; that there are many gradients. In addition, it is known that the relative reactivity of the smooth musculature of the blood vessels is by no means a criterion of the relative reactivity of other tissues.

Such studies of the reactivity of the patient are by no means of purely theoretical interest. It is true that the subject of inflammation per se, having progressed through cycles of interpretation from the periods purely speculative to the period of intensive objective research, from which it is just emerging, seems, perhaps because of the very mass of accumulated information, now in danger of being submerged in metaphysical abstractions or a one-sided insistence on relatively unimportant detail. This is unfortunate, because inflammation should be a subject for clinical, never philosophic, study.

Partly, the difficulty is to be sought in the fact that the purely histologic concept of pathology is no longer adequate to the pace of the correlated sciences. Pathology is stepping from cellular to molecular changes and histology must make ever greater use of chemical and physical tools. Partly, the reason is to be sought in the definite realization of an all-embracing interrelation and integration of cell and organ functions that make up the totality of the person. While, therefore, the interests of investigators must center on ever smaller objects as they approach molecular pathology, these interests must, at the same time, become wider as they include constitutional pathology, the study of the functional reactions of the entire organism. It is no longer possible to expect a satisfying solution of problems unless the range of the inquiry is so extended.

Schade² led the way in bringing together much of the pioneer work that underlies molecular pathology. The entire range of subjects grouped together as pathologic physiology forms the real background. Particularly, the chemical correlations of the Kraus school,³ in which the effort has been made to associate every-day medical problems with the chemical status of the individual person, seem to us to have been of greatest value. They took origin in earlier work of American physiologists. When one turns to problems of constitution,

1. Eppinger, H., and Hess, L.: *Ztschr. f. klin. Med.* **68**:205 and 230, 1909.

2. Schade, H.: *Physikalische Chemie in der innere Medizin*, ed. 3, Dresden, Theodor Steinkopff, 1923.

3. Kraus, F.: *Allgemeine und spezielle Pathologie der Person: I. Tiefenperson*, Leipzig, Georg Thieme, 1926.

it is particularly Bauer⁴ who has emphasized the practical value. In this country, it is Draper⁵ who has sought to extend a wider appreciation of the medical importance of constitutional reactivity.

It is inflammation with which one is, after all, chiefly concerned. Whether one studies it in its physiologic approaches, as one can very readily in digestive activity, whether in the exaggerated or peculiarly modified manifestations apparent in allergy, whether in default, as it may be in severe infections, the fundamental components that control the phenomenon must be similar, must be amenable to control and, therefore, must be therapeutically approachable by other than specific measures. The fundamental components engaged include the local cell mass, the mobile cells, the vascular tissues, the autonomic nerves and the chemical and hormonal influences of the humoral milieu. The innumerable variations possible with so many variable factors operative in the process readily account for the different types of inflammatory reactions with which one has to deal clinically.

The emphasis on the etiologic factor in inflammation which resulted from the development of bacteriology, for a time over-shadowed any interest in factors that might inherently modify the inflammatory reaction. Only in relatively recent times does one find investigation dealing, for instance, with the modification of inflammation as the result of preexisting inflammatory processes (tuberculosis, for example), the change in the blood chemistry under such conditions or the gradual alteration of the autonomic responses.

The particular studies that are made the basis for this, as well as the subsequent related papers, have as their background the considerations outlined in the preceding paragraphs. We have taken a group of 100 so-called normal men and have endeavored to see what relation their reactions to a stimulus or an injury—blister, Kromayer lamp burn, ice, injection of epinephrine hydrochloride, pharmacologic intracutaneous injections, etc.—might bear to previous disease (tuberculosis, syphilis, infections), the blood chemistry, the basal metabolic rate, the age, the weight, etc.

There are many factors that limit the value of conclusions drawn from such work. In the first place, averages made from only 100 individual reactions are by no means satisfactory. The normal individual variations in many of the reactions are large. The possibility of error in the determination of many of the reactions themselves cannot be excluded, chiefly in such determinations as that of the basal metabolic rate. The practical inability to secure duplicates, due to the

4. Bauer, J.: *Konstitutions und Vererbungslehre*, ed. 2, Berlin, Julius Springer, 1923; *Klin. Wchnschr.* 8:145, 1929.

5. Draper, George: *Human Constitution*, Philadelphia, W. B. Saunders Company, 1924.

fact that only one examination was feasible and that the amount of blood that could be taken without arousing resentment was limited, does not afford the feeling of accuracy that we might desire. These were factors that we could not alter, however much we might deplore them.

The persons examined were presumably "normal" men. That is to say, they were not patients of the hospital. About twenty were men employed about the hospital and laboratories as technicians, the rest were unemployed men who were sent to us from the state employment bureau. They ranged in age from 20 to 76; some were undernourished, some were chronic users of alcohol. A large percentage showed definite evidence of cardiorenal vascular damage of some degree. We felt that the group afforded us sufficient variation in reactivity because of their environmental conditions. We have not included women in the study lest the profound biologic alterations associated with the sex cycle⁶ should introduce more factors difficult to evaluate and control.

EXAMINATIONS MADE

The men reported to us at eight in the morning, having been instructed to come without breakfast. In a few instances, they had had alcoholic stimulants the night before. Some were apprehensive and nervous, and the examination of the basal metabolic rate was undoubtedly unsatisfactory on that account. They were kept under observation the entire day, during which they were given a luncheon at noon.

The examinations made included the following:

1. The blood chemistry: calcium by the method of Clark and Collip;⁷ potassium by the method of Kerr;⁸ CO₂ combining power; sugar (Folin-Wu); cholesterol by the Bloor, Pelkan and Allen^{8a} modification of the Bloor method; globulins by the method of Rohrer,⁹ and total protein by the refractometric method.

2. The skin blister by the cantharides method,¹⁰ with determination of the relative permeability of the capillaries, and determination of the blister time.

6. Petersen, W. F., and Milles, G.: The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, *Arch. Int. Med.* **38**:730 (Dec.) 1926.

7. Clark and Collip: *J. Biol. Chem.* **63**:461, 1925.

8. Kerr, J.: *Biol. Chem.* **67**:689, 1926.

8a. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: *J. Biol. Chem.* **52**:191, 1922.

9. Rohrer: *Deutsches Arch. f. klin. Med.* **121**:221, 1926.

10. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch. Int. Med.* **38**:663 (Dec.) 1926.

3. The basal metabolic rate and the weight/length ratio (weight in pounds, length in inches).

4. Reactions to the subcutaneous injection of epinephrine hydrochloride, as shown by pulse rate and blood pressure. In the charts, the increase or decrease in the average pulse pressure for one hour after the injection is recorded in terms of the percentage of the pre-injection level. A calculation was also made of the so-called cardiac output (pulse pressure \times pulse rate), and the percentage of increase or decrease recorded.

5. The reaction to the Kromayer lamp, as shown in the time of appearance of erythema following an application of the light for thirty seconds to the forearm.

6. The reaction to ice, as revealed in the time of appearance of erythema following an application of ice to the chest wall.

7. The muscle reactions, as shown by the threshold of electric current that would provoke reactivity, in milliamperes.

8. The resistance of the moist skin for direct current of low amperage. This was determined in the following way:

A storage battery (fig. 1) of a potential difference of 2 volts was short circuited by a potentiometer of 730 Ω . From one terminal and the sliding contact of the potentiometer, a variable voltage could be taken between 2 volts and zero and measured by a scale along the potentiometer wire. This voltage was applied to the skin by two clay electrodes, soaked with 1 per cent saline solution. The larger electrode was kept firmly by the left hand of the patient, the smaller electrode was placed on those parts of the left arm the resistance of which was to be determined (from two to three on the front). Usually points close to the center of the biceps and those between the elbow and the wrist at the flexor side were selected. The resistance between the large electrode and the hand was negligible against the much larger resistance between the small electrode and the spots on the arm. Any contact between the smaller electrode and an open wound made it evident that the resistance of the lower tissues (muscle, blood vessels, etc.) was small as compared with the resistance of the skin. A micro-amperemeter was inserted in this circuit, one scale division registering 0.24 microampere. All the readings were taken at scale division 10, i. e., 2.4 microamperes, by adjusting the potentiometer till this constant current was reached. This method employing constant current was preferable to the one employing constant voltage, because the resistance of the skin varied considerably, and sometimes, even with a low voltage, so much current was going through as to cause a burning, stinging pain; in this case, the current showed a tendency to go up gradually. In preparation for the measurements, the skin was wet with saline solution and then dried gently, and the wet electrode put on. The voltage was increased from zero to the one which gave a micro-amperage of 2.4. Exceptionally, the maximal voltage failed to cause the desired current to flow. In this case, the resistance was figured out from the voltage 2 and the current of less than 2.4 microamperes. Our figures for resistance are given in terms of megohms per square centimeter. Usually five spots on the biceps and five spots on the lower arm were measured. The measurements were made from three to

four times on the same day, early in the morning, right before and right after lunch and possibly later in the afternoon. This was important in order to get averages, and to gain an idea as to the variations that occur in the course of a day.¹¹ We have started investigations with the point of view of following up these variations of resistance more closely and in relation to other factors.

9. The reactions to intracutaneous injections (Hecht-Groer), as estimated by the average size of the wheal (diameter in millimeters) and

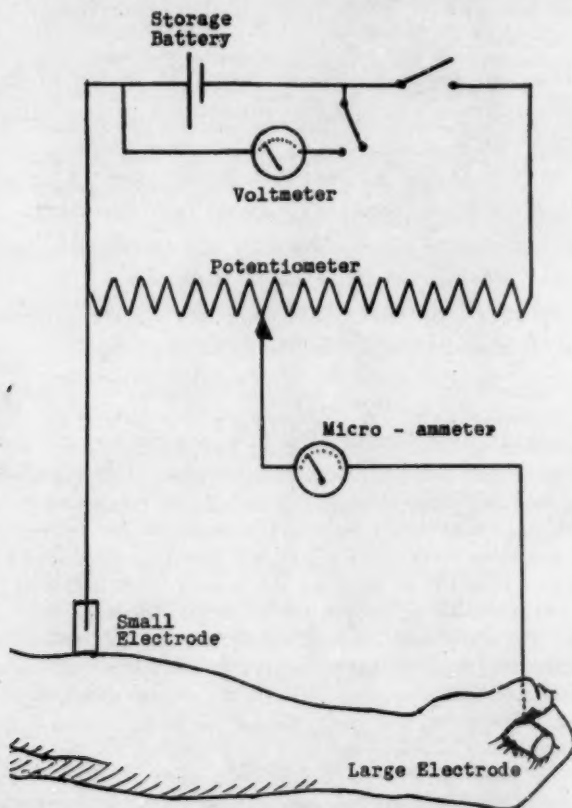


Fig. 1.—A diagram showing the method used in testing the resistance of the skin to electric current of low amperage.

11. Some measurements were repeated the next day or a few days later, in order to control variations that might occur from day to day. Extensive measurements of this kind were reported by Curt P. Richter (*The Electrical Skin Resistance: Diurnal and Daily Variations in Psychopathic and in Normal Persons*, *Arch. Neurol. & Psychiat.* **19**:488 [March] 1928). Richter found characteristic diurnal variations for certain classes of neurologic patients; daily variations occurred also, but they were small compared to the pronounced differences of the average resistance from one to another patient.

the flare (width of radium in millimeters) for: (a) morphine (1 to 10,000,000 and 1 to 1,000,000); (b) epinephrine hydrochloride, 1 to 1,000, 1 to 10,000, 1 to 100,000 and 1 to 1,000,000; (c) thyroxin, 1 to 10,000, and (d) caffein, 1 to 100.

10. A roentgenogram of the chest to ascertain the presence of active or healed tuberculosis and the condition of the great vessels and heart.

11. A physical examination and history, particular emphasis being laid on a history of sensitization and of previous infectious diseases, alcoholism, the amount of hard physical labor, etc.

12. A Wassermann test.

13. A urinalysis and examination of the skin capillaries.

METHOD OF ASCERTAINING CORRELATIONS

In order to obtain a general survey of the large amount of statistical material obtained, we proceeded in the following manner:

The results of each determination were arranged in arithmetical order. For instance, the individual cases were first arranged in the order of the time required for the formation of the blister, which varied from 3.5 to 15 hours. Four groups (twenty-five each) were then made, and the averages determined, the averages in this case being 5.8, 6.2, 7.9 and 10.2 hours. The averages were then recorded, and averages were determined and recorded for the results of the other examinations of the men thus grouped in order of increasing blister time. For instance, the corresponding averages for the time of the reaction to the application of the Kromayer lamp were found to be 1.27, 1.92, 2.4 and 2.36 hours, respectively, a sequence which might justify the supposition that some common factor is to be sought in the apparent coincidence of delay in the formation of the blister and delay in the appearance of the erythema. If, on the other hand, the averages for the results of the other examinations revealed no consistent progression or regression, we felt justified in assuming that no important correlation existed.

In table 1, we therefore present the average figures for each determination arranged in sequence, the four figures in each compartment indicating the averages of the four groups of twenty-five each.¹²

The heavy arrow has been inserted to show the direction of progression of the values for each key subject under consideration. Thus, column 1 indicates the average blister time of the four groups, and in reading down, the averages for the other determinations will be found. The lighter arrows indicate a probable correlation with the key sub-

12. Only the group arrangements for the flares of the reactions to thyroxin and caffein differ. Fifty-six persons have no thyroxin flares; the results for the rest were arranged in sequence. Sixty-four persons showed no caffein flares. The results for the thirty-six who showed flares were arranged in sequence in three groups of twelve each.

ject under consideration. Thus in column 1 some apparent relation exists between the calcium level, the potassium level, the K/Ca ratio, etc., and the subject under consideration, i. e., the blister time.

BLISTER TIME (TABLE 1, COLUMN 1)

The average blister time for the 100 men was 7.5 hours. In previous communications,¹³ we called attention to the fact that the blister time of a person may vary considerably, being uniformly short in the exophthalmic patient and prolonged in patients with certain types of renal disease. In our use of the method, the plaster was removed after six hours, and the time of appearance of the blister recorded on the basis of the time from the application of the plaster to the time when the first evidence of blistering was observed. A shortening of the blister time was apt to be overlooked by this practice, and our records, therefore, are more accurate for the cases showing prolonged blister time than for those showing a shortened blister time.

The averages of the blister time (in hours) for the four groups, as recorded in table 1 are:

5.8 6.2 7.9 10.2

Certain correlations with other determinations appear as follows:

Kromayer Lamp Reaction Time.—The groups that had a long blister time showed a delay in the appearance of the erythema following application of the Kromayer lamp for 30 seconds, as follows (hours):

- 1.27 (ranging from 45 min. to 3 hrs.).
- 1.92 (ranging from 50 min. to 5 hrs., 50 min.).
- 2.4 (ranging from 1 hr., 10 min. to 8 hrs.).
- 2.36 (ranging from 1 hr., 25 min. to 4 hrs., 50 min.).

As the erythema is probably due to the liberation of toxic substances from the injured cells of the skin area (Lewis¹⁴), one might anticipate some correspondence. The agreement of the two reactions is confirmed when the cases are arranged according to the Kromayer lamp reaction time (column 9).

Basal Metabolic Rate.—With increasing blister time, the basal metabolic rate is lowered, but the sequence of regression is not perfect:

11.8 5.9 (9.8) 5.3

A general agreement with this trend is found in column 10.

13. Petersen, W. F.: The Permeability of the Skin Capillaries in Clinical Conditions, *Arch. Int. Med.* **39**:19 (Jan.) 1927.

14. Lewis, Thomas: *Blood Vessels of the Human Skin and Their Responses*, London, Shaw & Sons, 1927.



TABLE 1.—The Correlations of Reactions Determined

Average		Blister	Permeability	Inflammatory Index	Calcium	Potassium	K/Ca Ratio	Sugar	Alb./Glob. Ratio	Kromeyer	Basal Metabolic Rate	Skin Resistance	Muscle Reaction	Systolic Blood Pressure	Pulse Rate
7.5	Blister Time (hours)	5.8 7.3 10.2	7.5 7.3 8.1	10.6 7.3 9.1	7.7 7.9 9.1	8.7 8.6 9.1	8.8 8.7 8.8	7.2 7.3 7.3	9.7 7.4 7.4	6.9 7.7 8.6	8.5 7.7 7.6	7.7 7.2 7.8	7.6 7.2 7.8	8.1 7.3 7.9	8.7 7.4 8.3
62.	Permeability Ratio	58. 67. 64.	52. 58. 75.	63. 62. 71.	63. 62. 62.	63. 62. 62.	61. 60. 58.	60. 68. 60.	60. 67. 64.	61. 63. 62.	65. 59. 54.	60. 61. 67.	62. 62. 64.	64. 63. 59.	64. 64. 60.
8.2	Inflammatory Index	9.7 8.1 6.1	7.4 7.8 10.4	5.7 9.4 10.9	9.5 9.24 9.6	8.1 8.5 8.6	7.6 9.2 9.2	8.9 9.7 7.6	7.4 9.3 7.6	9.7 8.5 8.5	8.5 8.8 8.2	8.5 8.9 8.9	10.1 9.3 9.06	8.8 8.4 8.3	8.7 9.1 7.4
10.17	Calcium (mg.)	10. 10.1 10.5	9.8 10.1 10.3	10.2 10.1 10.2	8.2 10.8 12.2	10.3 9.9 9.6	11.8 9.2 9.2	9.9 10.4 10.4	10. 10.2 9.8	10.3 10.1 9.7	9.6 10.1 8.4	9.9 10.3 10.1	9.9 9.9 10.3	9.8 10.3 10.	9.9 10.5 10.1
20.4	Potassium (mg.)	20.6 21.4 20.3	19.6 20.6 19.7	19.1 19.1 20.9	19. 21. 19.2	16. 18.2 25.7	16.8 18.6 24.5	19.7 19.5 19.9	19.7 20. 19.6	20. 20.2 19.6	19.7 20.5 20.8	20.1 20.9 19.7	20.1 19.6 19.7	20.2 19.1 19.4	19.1 20.3 20.
2.	K/Ca Ratio	2.09 2.09 2.03	2.06 1.95 1.93	1.91 2.08 2.03	2.3 1.82 2.03	1.58 2.08 2.56	1.45 1.81 2.68	1.9 2.2 1.9	1.97 2.08 2.08	1.99 2.02 1.9	1.95 2. 2.06	2.06 1.99 1.9	2.22 1.96 1.80	1.96 1.93 1.92	1.95 1.70 1.98
71.	Sugar (mg.)	71. 71. 71.2	70. 70. 70.	73. 70. 70.	67. 71. 73.	72.1 73.2 73.5	71. 72. 72.	60. 74. 72.	69. 72. 72.	70.9 72.4 68.9	70. 72.4 67.4	69.3 71.2 71.2	72. 73.2 70.5	70.4 74.4 68.1	69.9 70.9 70.7
2.	Albumin/Globulin Ratio	2.01 2.22 1.73	1.71 1.74 2.42	1.4 2.5 2.3	1.9 1.76 2.2	1.84 2.20 1.88	1.89 1.8 2.1	1.86 1.73 2.1	1.1 1.6 3.3	1.86 2.10 2.03	2.1 1.93 1.76	1.9 1.96 2.10	1.65 1.89 2.08	1.84 1.84 1.74	1.95 2.22 1.48
2.	Kromeyer Time (hours)	1.27 1.92 2.3	2.02 2.56 2.03	2.24 1.81 1.92	1.85 1.97 1.92	1.86 2.08 2.1	2. 2.09 2.32	2.1 1.93 1.94	1.87 2.22 2.32	1.24 1.58 1.9	2.25 2.06 2.08	1.8 2.01 2.73	2.16 2.13 1.96	1.86 2.35 2.34	2.4 1.8 2.01
+ 8.	Basal Metabolic Rate	11.8 9.9 9.8	10. 8.5 4.8	8.3 10. 10.	12.8 9.3 13.2	16.7 7.4 12.	11. 7.4 12.	13. 8.5 7.2	8.4 9.4 9.4	9.7 12.4 8.1	8.9 13.3 28.	13. 4.5 9.4	8.4 8.4 9.4	12.5 8.1 9.5	6.4 8.4 9.4
.46	Skin Resistance (M. Ω)	.51 .38 .53	.44 .44 .40	.37 .44 .48	.33 .48 .63	.46 .46 .37	.65 .46 .36	.52 .44 .43	.31 .46 .46	.48 .39 .62	.47 .39 .3	.14 .27 1.03	.47 .65 .38	.43 .49 .47	.51 .35 .47
3.2	Muscle Reaction (M.A.)	3.3 3.23 3.2	3.4 2.5 3.5	2.85 2.23 2.23	3.4 2.68 3.3	3. 3.4 2.66	3.1 3.8 3.2	2.8 3.26 2.9	2.9 3.6 4.0	3.2 3.6 2.7	3.2 3.6 3.3	3.6 3.6 2.7	1.7 2.8 3.7	2.8 2.9 3.7	4.1 3.2 2.36
124	Systolic Blood Pressure	125. 121. 127.	126. 128. 122.	126. 124. 122.	123. 124. 122.	128. 125. 127.	125. 114. 122.	124. 123. 113.	125. 124. 122.	125. 124. 124.	123. 124. 123.	123. 120. 119.	124. 121. 124.	104. 118. 146.	125. 112. 126.
71.	Diastolic Blood Pressure	71. 71. 70.	72. 67. 72.	72. 67. 71.	70. 73. 68.	70. 72. 70.	72. 72. 72.	71. 71. 75.	72. 72. 70.	72. 70. 69.	72. 70. 67.	72. 70. 67.	71. 72. 70.	62. 72. 72.	71. 69. 74.
72.5	Pulse Rate	70. 72. 74.	74. 70. 73.	76. 70. 72.	71. 73. 76.	75. 71. 75.	77. 72. 73.	72. 73. 73.	72. 74. 66.	67. 75. 72.	72. 75. 72.	72. 74. 72.	74. 78. 74.	70. 75. 70.	60. 69. 58.
53	Pulse Pressure	55. 50. 54.	55. 53. 50.	54. 57. 51.	51. 52. 62.	58. 52. 55.	53. 49. 56.	53. 56. 54.	53. 52. 52.	53. 54. 55.	53. 54. 52.	51. 54. 51.	59. 53. 54.	53. 48. 58.	54. 44. 56.
+ 14.4%	Epinephrine, Pulse Pressure	16.3 16.3 10.6	9.4 16. 17.	10.2 11. 17.	13. 13.7 13.	9.4 18.6 16.3	7.5 14. 14.	8.5 12. 12.	13. 15. 12.	16. 13.2 10.2	16. 15.7 13.3	11. 14. 14.	11. 14. 11.	21. 12. 9.9	21. 10.8 13.
+ 20.5%	Epinephrine, Pulse Pressure x Pulse Rate	21. 25. 23.	14.6 22. 24.	12. 22. 25.	33. 20.2 21.7	15.4 16.8 23.2	14.6 21. 24.	13. 21. 29.	18. 16. 23.	25. 21. 17.8	16. 24. 16.6	16. 22. 23.	16. 22. 19.	27. 29. 16.	29. 21. 18.
57.7	CO ₂ Combining Power	57. 60. 57.3	56.6 59.1 57.8	57.3 57. 58.	57.8 57.5 57.9	56.7 56.5 58.9	57. 57.8 58.2	57.9 57.5 57.9	57.8 57.5 57.9	57.8 57.5 57.9	57.8 57.5 57.9	57.8 57.5 57.9	57.8 57.5 57.9	57.8 57.5 57.9	57.8 57.5 57.9
19.	Ice Reaction (seconds)	16. 20. 21.	18. 23. 19.4	20. 20. 19.	16. 22.4 20.8	19. 18. 20.	21.8 16.8 18.1	17.4 15.8 18.1	19. 20. 17.	19. 17. 18.4	16.3 17. 20.4	22. 19.3 20.	19. 20. 20.	19. 15. 20.	19. 19. 21.
46.5	Age	46. 44. 43.	51. 46. 41.	55. 47. 39.4	48. 46. 40.	50. 46. 45.	51. 47.6 47.8	50. 44. 48.	49.4 47. 46.	46. 46. 48.	46. 45.7 47.	46. 46. 46.	46. 46. 46.	46. 46. 46.	47. 43. 50.
217	Weight/Length Ratio	220. 230. 213.	229. 233. 216.	227. 222. 217.	218. 219. 212.	214. 223. 216.	206. 217. 222.	211. 217. 220.	221. 221. 218.	221. 221. 210.	221. 221. 210.	221. 221. 210.	221. 221. 210.	221. 221. 210.	221. 221. 210.
207	Cholesterol (mg.)	231. 173. 215.	228. 230. 214.	218. 217. 226.	217. 203. 227.	208. 222. 222.	215. 220. 229.	208. 220. 218.	207. 220. 220.	231. 220. 218.	220. 220. 218.	220. 220. 218.	220. 220. 218.	220. 220. 218.	220. 220. 218.
19.2	Epinephrine, Wheal (m m.)	22.2 18.8 19.6	20. 19.6 20.0	19.6 13.2 20.24	17.2 19.2 20.	19.2 20. 19.6	20.4 20.6 20.	19.4 17.6 19.6	19.6 18.4 20.	20.4 20.4 18.4	19.2 20.4 15.2	20. 20. 15.6	19.6 20. 20.4	19.6 19.6 19.6	19.2 19.6 19.2
8.8	Epinephrine, Flare (m m.)	8.4 8.8 8.8	8.4 9.0 8.2	8.6 8.6 9.4	8. 9.2 10.	8. 8.6 9.4	8.4 8.4 8.6	7.6 8.4 8.6	8. 8.2 9.2	9.2 9. 8.2	8.4 9.8 8.4	8.4 9.8 9.6	8.4 9.8 9.6	8.4 9.8 9.6	8.4 9.8 9.6
12.4	Morphine, Wheal (m m.)	11.2 11.8 11.	12.8 12. 11.2	11.2 11.6 12.4	10.8 12. 11.4	11.6 12. 11.4	11.2 11.2 11.	11.4 11.2 11.	11.6 11.6 11.4	12.2 11.6 11.4	10.6 11.6 10.4	11.6 11.6 10.4	11.6 11.6 10.4	11.6 11.6 10.4	12.2 11.8 16.4
15.6	Morphine, Flare (m m.)	15.4 16.2 15.6	15.8 16.4 16.	15. 16.2 15.	14.2 15.2 16.6	15.6 15.2 16.	16.4 15.2 15.6	17.4 17.6 15.6	14. 17.6 15.6	15.6 16.4 15.	15. 16.4 14.2	15. 16.4 14.2	15. 16.4 14.2	15. 16.4 14.2	15.6 16.4 15.2
11.2	Thyroxin, Wheal (m m.)	11. 9.4 10.2	11.4 11.5 11.	12.6 10.6 10.6	12.2 11.2 12.	12.2 11.4 10.6	12.4 11.4 10.6	12. 10.8 10.6	11.6 11.6 11.6	11.2 11.6 11.6	11.2 11.6 11.6	11.2 11.6 11.6	11.2 11.6 11.6	11.2 11.6 11.6	11.2 11.6 11.6
4.8	Thyroxin, Flare (m m.)	4.6 3.4 5.6	4.4 4.6 5.2	4. 4.6 5.2	5.6 4.4 5.2	6.4 4.4 5.2	6.6 4.6 5.2	5.4 4.6 5.2	3.8 4.4 4.2	3.2 4.4 5.6	6.8 5.2 3.6	3.4 5.2 3.6	5.2 5.2 3.6	4.8 5.2 3.6	4.8 5.4 3.8
17.6	Caffeine, Wheal (m m.)	19.2 14. 20.	17.4 18.2 19.	17.2 18.2 15.4	21. 14.8 16.6	20. 17.6 11.	21.6 18.2 15.4	21.2 17.6 17.4	16.8 18.4 19.2	18. 15. 18.4	19.2 15.6 17.4	18. 15.6 18.2	18. 15.6 18.2	18. 15.6 18.2	18. 15.6 18.2
2.7	Caffeine, Flare (m m.)	2.4 1.8 2.6	1.4 3.4 2.8	2.8 2.8 2.8	3.4 1.4 3.2	2.8 4.8 1.6	2.8 3.2 1.	2.8 3.2 1.	1.6 2.8 2.4	1.6 4.8 2.	2. 4.6 1.4	2. 4.6 1.4	2. 4.6 1.4	2. 4.6 1.4	2. 4.6 1.4

1 2 3 4 5 6 7 8 9 10 11 12 13 14

Continued in a Study of One Hundred "Normal" Men

Pulse Rate	Epinephrine, Pulse Pres- sure	Epinephrine, Pulse P. Pulse Rate	CO2 Combining Power	Ice Reaction	Age	Weight/Length Ratio	Cholesterol	Epinephrine, Wheal	Epinephrine, Flare	Morphine Wheal	Morphine Flare	Thyroxin Wheal	Thyroxin Flare	Caffein Wheal	Caffein Flare
8.4	59.7	63.3	7.8	7.3	6.9	8.4	7.7	6.9	7.6	7.2	8	7.1	6.4	6.9	7.2
7.2	59.7	63.3	7.5	7.3	6.9	7.1	7.5	7.5	7.6	8.2	7.7	7.6	7.5	7.5	8.2
8.3	59.7	63.3	7.4	7.3	6.9	7.5	8.2	7.5	7.8	7.3	8.2	8.3	8.2	7.8	7.4
14.4	59.7	63.3	82	64	69	63	64	62	60	62	62	60	60	60	60
12	59.7	63.3	58	61	62	61	62	63	63	64	62	62	63	63	64
10	59.7	63.3	67	65	60	67	61	61	65	65	66	63	64	60	67
9.9	59.7	63.3	8.6	9.2	10.1	8	9.7	9.8	8.3	9	8.6	9.6	9.6	9.8	7.9
9.8	59.7	63.3	8.5	8.5	9.4	8.5	9.7	9.9	9.9	9.8	8.6	8.7	9.9	7.3	9.4
9.4	59.7	63.3	8.5	9.5	9.4	8.3	9.6	9.8	9.4	9.5	8.8	8.3	7.9	8	9.1
9.9	10.3	10.2	9.7	9.8	10.4	10.4	9.7	9.8	9.8	10.1	9.2	10.4	10.2	10.4	10.5
10.5	10.3	10.2	10.7	10.3	10.3	9.7	10.3	9.9	10.2	10.1	10.2	10.3	10.3	9.6	9.7
10.1	10.3	10.2	10.1	10.6	9.4	10.4	9.2	10.3	10.6	10.2	9.3	10.8	9.8	9.1	9.9
19.1	19.3	19.2	18.3	18.5	19.8	19.3	17.7	20.2	19.3	20.1	20.4	22.3	21.8	22.1	21.3
15.1	20.5	20.5	20.3	20.2	20.3	20.4	18.5	19.5	20.1	19.3	20.4	19.2	20.7	19.8	18.6
20	20.9	19.4	20.6	24.4	19	21	20.1	20.2	20.2	20	19.6	17.7	18.2	17.4	19
1.96	1.88	1.85	1.88	1.89	1.99	2.01	1.84	1.96	1.89	2.08	2.05	2.22	2.12	2.21	2.2
1.99	2.01	2.06	2.06	1.96	2.09	2.08	1.82	1.86	2.16	2.03	1.97	1.83	1.92	1.94	1.94
1.9	1.99	1.96	1.96	2.04	2.14	1.82	2.08	1.85	1.92	1.89	1.87	1.89	1.97	1.94	1.94
1.98	2.03	1.95	2.04	2.14	1.82	2.01	1.84	1.92	1.82	1.99	2.08	1.82	1.74	1.73	1.71
59.9	69.1	68.6	69.7	68.6	65.5	69.5	69.3	71.4	68.3	69.8	70.2	67	71	74	71
59.5	71.1	70.2	72.2	71.9	74.1	69.2	69.8	71.3	70.6	71.7	67.3	68.4	74.4	68.8	73
79.9	70.9	72.8	72	72.8	74.3	72.4	69.6	68.8	73.2	71.7	70.5	68.2	72.1	67	69.6
1.95	1.94	1.9	1.84	2	2.21	1.74	1.79	1.92	1.89	1.94	2.13	1.72	1.75	1.67	1.95
2.22	2.14	1.91	1.92	2.02	2.02	2.21	1.84	1.92	1.83	2.20	2.14	1.83	2.12	2.26	2.33
1.4	1.9	1.81	1.83	1.97	1.60	1.89	1.93	1.93	2.08	1.98	1.96	2.11	2.19	2.01	1.86
2.48	1.85	1.76	1.80	1.96	1.90	2.21	1.97	2.14	2.13	2.30	2.49	2.27	1.9	2.16	2.08
2.04	2.04	2.13	1.83	2.15	2.12	2.12	1.95	2.03	1.87	1.76	2.04	2.10	2.04	2.30	2.03
2.1	2.1	2.12	2.3	2.24	2.07	2.01	2	1.9	2.01	1.93	1.92	1.91	2.03	1.48	1.92
6.4	9.6	6.9	13	8.6	7.8	9.9	12.3	12.4	13	6.6	8.4	10.4	6	8.2	7.8
8.9	7.2	8.9	6.3	7.8	8.4	10.1	8.5	10.5	10.4	14.2	12.1	13	8.6	12.1	6.8
8.4	10.5	13	8.9	12.5	13.5	6.9	7.4	10.5	7.3	6.9	8.5	5.1	8.6	5.8	9.6
51	38	37	45	38	53	66	28	50	29	41	40	49	49	41	41
36	39	53	35	43	33	43	63	37	47	40	35	33	33	37	38
51	38	38	58	42	40	42	26	41	42	43	35	42	40	43	65
44	42	53	41	47	20	20	20	61	63	43	52	51	52	56	60
4.1	3.17	2.4	3.7	3.7	2.9	2.39	2.6	2.8	3.45	2.6	3.10	3.04	3.10	2.8	3.1
3.07	3.1	3.9	3.4	3.19	3.1	3.45	2.9	3.3	3.09	3.4	3.04	3.28	3.3	3.2	2.8
2.36	2.8	3.15	3	3	2.4	3	2.9	3.04	3.05	3.2	3.28	2.9	3.4	3.3	2.6
25	124	127	127	122	112	121	128	119	129	121	132	123	124	128	128
12	126	125	118	120	124	120	124	119	121	127	122	122	122	121	122
25	127	125	117	122	124	121	125	120	124	120	120	119	123	122	122
26	115	124	115	122	128	128	121	121	124	123	126	119	123	121	106
71	70	68	73	70	68	68	68	68	69	69	71	71	70	69	72
68	72	73	70	72	73	70	65	69	68	66	67	67	66	64	72
69	73	70	68	67	72	68	73	70	70	71	72	72	72	70	68
64	76	74	74	67	74	76	70	73	72	74	73	73	72	74	73
69	68	70	74	70	74	68	70	73	70	74	71	70	66	65	73
96	73	76	73	73	71	72	72	71	69	71	70	70	72	73	72
54	54	59	54	52	53	53	60	51	64	52	61	52	54	51	57
44	56	62	48	50	51	53	59	50	53	61	51	55	57	56	54
56	40	54	44	55	60	53	52	56	54	48	53	47	51	52	34
21	3.5	2	11	9	13	12	12.7	14	10	10	13	15	16.6	17	16.6
13	12	12	13	14	17	14	7.6	10	9	12	10	9	11	18	10
10.8	16	17	15	14.8	12	15	12	15	19	13	13	13	11	9	8
29	1	1.7	18	16	21	19	18.7	20	15	12	19	17	21	25	20.4
17	1	1.7	18	16	21	19	18.7	20	15	12	19	17	21	25	20.4
16	1	1.7	18	16	21	19	18.7	20	15	12	19	17	21	25	20.4
57.6	57.3	57.4	58.5	58.7	57.5	58.5	56.7	56	57.8	57.8	58	58	58.3	53.6	58
58.8	57.3	57.8	58.5	58.7	57.5	58.5	56.7	56	57.8	57.8	58	58	58.3	53.6	58
55.1	57.3	57.8	58.5	58.7	57.5	58.5	56.7	56	57.8	57.8	58	58	58.3	53.6	58
19	19	21	17	19	18	18	21	22	21	21	19	21	20	21	17.8
19	19	18	20	19	17	17	21	19	18	20	20	19	17	21	16
19	18	20.4	19	20	18	18	21	18	21	18	17	17	17	23	24
21	20	18	19	32	44	47	50	47	43	46	50	41	47	39	46.6
47	45	46	49	48	48	47	50	47	43	46	50	41	47	39	46.6
42	45	46	49	48	48	47	50	47	43	46	50	41	47	39	46.6
50	47	46	44	49	49	46	50	47	43	46	50	41	47	39	46.6
208	225	214	229	223	212	207	209	216	215	219	217	219	225	218	216
206	216	220	218	223	212	207	209	216	215	219	217	219	225	218	216
211	219	219	216	223	215	216	222	219	226	222	219	227	227	220	222
222	197	213	212	215	219	232	221	221	202	220	227	209	201	208	207
222	232	215	227	212	210	217	181	210	222	218	221	214	183	216	221
208	213	215	214	233	229	217	219	238	214	225	218	220	250	213	230
221	233	224	221	203	229	216	183	217	217	213	212	213	214	223	215
235	203	216	231	226	213	225	238	238	217	220	212	213	214	223	215
19.2	20	19.6	20	19.2	19.2	18.8	18.4	16.8	19.8	19.2	19.2	20.4	19	20.8	19.3
18.6	19.2	18.8	18.4	19.2	19.2	18.8	17.2	17.6	19.6	20.4	20.4	19.6	20	19.2	19.2
20	20	20.4	19.6	19.2	19.2	19.6	19.6	20.4	20	19.2	20.4	19.6	19.2	18.4	18.8
18.4	19.2	19.2	20.8	19.2	21.2	20	18.8	22	19.2	18.8	18.4	18.4	18.4	18	18.6
9.2	9.2	8.6	9.2	8.8	10.2	8.4	8.2	9	8.8	8.2	7.8	10	8.6	9.2	8.55
8.6	8.6	8.6	9.2	8.4	9.2	9	8.6	8.6	9.2	9.2	10	8.6	8.6	8.4	10
8.2	9.4	9.6	9.2	9	7.8	8.6	8.6	8	11.6	9	10	7.8	10	8.2	9
12.2	11.2	10.8	11.2	12.2	11.4	11	11.4	10.8	11.4	9	11.6	11.4	14.8	11.6	12.6
10.6	11.4	11.6	11	11.6	12	11.2	10.2	11.2	11.2	10.6	11.6	11.6	10.2	11.2	11.6
11.8	11.6	11.2	11.6	11.8	11.4	11.2	11.6	11.6	12.2	11.8	11.4	11.2	10.6	11.6	12
19.4	11.2	10.8	11.8	11	10.8	12.2	11	10.6	11.4	14	11.4	11.2	10.4	11	12.4
15.6	14.8	14.8	16	16	16.6	14.8	14.8	15.6	13.2	16.6	10	16.6	15	15.4	15
14	15.8	15.8	16.6	16.6	19.4	16.6	14.8	15.6	15.8	15.8	14.4	16.2	16	15.6	16
17.8	16	16.2	14.8	15	15.6	16.6	14	14	16	15.2	16.6	15	14.2	16	18
15.2	16.6	16.8	15	15.6	18	15.6	14.8	14.8	16.6	15	15.2	16.6	14.2	16	18
10.2	11.4	11.6	12	11.4	10.8	12.2	13.2	11.2	11.8	10	11.8	10.4	15.8	8.2	14.1
12.2	11.6	11.4	11.2	11.2	11.2	10.2									



Age.—Age plays some rôle, the group showing the prolonged blister time being somewhat older, although the individual variations in the four groups are large:

46 yr.	44 yr.	43 yr.	53 yr.
(26-68)	(25-66)	(28-79)	(22-73)

When the results are arranged on the basis of age (column 19), the oldest age group again shows prolongation of the blister time. It is to be kept in mind that the oldest age group will show greater vascular-renal damage.

Calcium, Potassium and K/Ca Ratio.—The prolonged blister time seems to be associated with a higher level of the blood calcium, as is evident in the following values:

10	10.1	10.1	10.5
----	------	------	------

The corresponding values for potassium are in inverted order:

20.6	21.4	20.3	18
------	------	------	----

The K/Ca ratio is, as a result, much lower in the group showing prolonged blister time:

2	2.19	2.01	1.71
---	------	------	------

Globulin.—The group with prolonged blister time also has the greatest amount of serum globulin. The corresponding averages for the albumin/globulin ratios are:

2.1	2.22	2.18	1.73
-----	------	------	------

This may be checked in column 8.

Summary.—An analysis of the material indicates that the group with prolonged blister time is somewhat older, has more globulin, more calcium and a lower K/Ca ratio and is less responsive to the Kromayer lamp.

PERMEABILITY (COLUMN 2)

The average index of capillary permeability for the entire group is 62. In our previous communications, we pointed out that the permeability of the capillaries, as measured by the blister method, is increased in certain persons, i. e., in those with exophthalmic goiter (13); in those with severe intoxications (13); in sympatheticotonic persons (15), etc. On the other hand, we noted that athletes tended toward a lower permeability (10), as did persons with certain types of lesions of the kidneys (13).

When the material now under consideration is grouped into the four groups of twenty-five each, the averages are found to be:

52	58	65	75
(46-56)	(56-61)	(61-70)	(70-91)

When the determinations are so grouped, the following correlations seem of interest:

Age.—Age apparently has a direct relation. The corresponding averages of the ages are:

51	50	46	41
(22-76)	(27-70)	(26-79)	(20-73)

It is obvious that all ages are represented in each group; nevertheless, the sequence is sufficiently good to seem of some significance (confirmed in column 19).

Weight.—Slender persons seemingly have the more permeable capillaries. The corresponding averages of the weight/length ratios are:

229	233	216	218
-----	-----	-----	-----

The confirmation in column 20 is good.

Reaction to Epinephrine.—In a previous paper,¹⁵ we showed that so-called sympathicotonic persons have an increased permeability of the capillaries. In this grouping, it may also be observed that with increasing permeability, there is increased sensitivity to epinephrine. The values for the pulse pressures on injection of epinephrine hydrochloride averaged (per cent):

+9.4	+16	+12	+17
------	-----	-----	-----

A confirmation of this appears in column 15.

Pulse Pressure.—With increasing permeability, the pulse pressure seems to diminish somewhat, the averages being:

55	53	54	50
----	----	----	----

corresponding to a slight decrease in systolic blood pressure.

Reactions to Intracutaneous Injection of Thyroxin and Caffein.—The flares of the reactions to thyroxin and caffein increase with increasing permeability (columns 27 and 29 may be compared with column 2 here).

Summary.—The apparent correlations are, therefore, with the age of the person, the weight/length ratio, the reaction to epinephrine, the pulse pressure and the radii of the thyroxin and caffein flares.

INFLAMMATORY INDEX (COLUMN 3)

In a previous study,¹⁰ we sought to define an inflammatory index on the basis of the two determinations just discussed, i. e., the blister time and the permeability of the capillaries. Presumably, the degree of inflammation might be regarded as most intense if the rapidity of the

15. Petersen, W. F., and Levinson, S. A.: The Relation of the Reaction to Epinephrine to Potassium-Calcium Ratio and Other Ratios, Arch. Int. Med. **42**: 256 (Aug.) 1928.

reaction and the degree of protein passage through the vessels were taken into consideration. We therefore used the ratio permeability/blister time as an index and used the term inflammatory index for the quotient.

The average inflammatory index of the 100 men is 8.2

$$\frac{62 = \text{average permeability}}{7.5 = \text{average blister time}}$$

The averages for the four groups are:

5.7	8	9.4	10.9
-----	---	-----	------

The blood chemical correlations are evident:

Potassium Level.—

19.1	19.1	20.8	20.9
------	------	------	------

K/Ca Ratio.—

1.9	1.9	2.06	2.03
-----	-----	------	------

CO₂ Combining Power.—

56.5	57.3	57.3	58
------	------	------	----

These correlations are confirmed in columns 5, 6 and 17, respectively, though the confirmation in the latter case in only partial.

Albumin/Globulin Ratio.—Only the group with the low inflammatory index seems to have an increased amount of globulin, the ratios being:

1.4	2.5	1.8	2.3
-----	-----	-----	-----

and this is confirmed when the tabulations for globulin are examined (column 8).

Other Correlations.—The relation of age (the inflammatory index decreasing with age) seems certain; the relation of the weight/length ratio (a higher inflammatory index being found in the more slender subjects) is doubtful because it is not confirmed in column 20; and the correlation with the reactions to epinephrine is also uncertain for the same reason (columns 15 and 16). On the other hand, the resistance of the skin to electric current increases with increase in the inflammatory index, while the Kromayer lamp erythema time has a reverse relation (confirmed in column 9).

Summary.—We seem to be justified in the assumption that the inflammatory reaction to cantharides is inhibited by advancing age and is more intense with higher levels of potassium and higher values of the K/Ca ratio. The Kromayer lamp reaction time is comparable. There is a probability that the more slender persons and the persons with the more marked reactions to epinephrines have a more intense inflammatory reaction. Curiously enough, there appear to be no correlations

with the intracutaneous reactions to pharmacologic substances except that to thyroxin. This diminishes with increase in the inflammatory index (column 26).

CALCIUM (COLUMN 4)

The average calcium value for the 100 men is 10.17. The average calcium values for the four groups are:

9.2	9.7	10.8	12.2
(from 7.4-9)	(from 9.2-10.3)	(from 10.4-11.4)	(from 11.4-14.5)

Blister Time.—The relation to the blister time has been discussed.

Sugar Level.—There appears to be some relation to the sugar level, the persons with low calcium level having a lower sugar level (confirmed in column 7). The differences are not, however, great:

67	73	71	73
----	----	----	----

Resistance of the Skin to Electric Current.—A relation to the resistance of the skin to electric current seems probable (although the confirmation in column 11 is not convincing):

0.33	0.48	0.42	0.63
------	------	------	------

Reaction to Ice.—With an increasing amount of calcium, the reaction to ice is retarded (confirmed in column 18):

16	16.8	22.4	21.5
----	------	------	------

Pulse Rate, Systolic Blood Pressure, and Pulse Pressure.—With increasing amounts of calcium, the pulse rate increases:

71	73	71	76
----	----	----	----

but the confirmation in column 14 is not good. The systolic blood pressure increases as follows:

121	123	122	129
-----	-----	-----	-----

but here, again, the confirmation (column 13) is not clear. The increase in the pulse pressure is more marked:

51	50	52	62
----	----	----	----

As no tabulation was made on the basis of pulse pressure, no confirmation is possible.

CO₂ Combining Power.—A possible correlation exists with the CO₂ combining power, which increases as follows:

56.4	57.8	57.5	57.9
------	------	------	------

These differences are not great, but appear to be confirmed in column 17, where the calcium values increase with increasing CO₂ values.

Skin Reactivity.—The calcium column is the first in which we begin to find some correlations with the reactions of the skin to injections of pharmacologic substances. The wheal caused by the injection of epinephrine hydrochloride increases progressively as follows:

17.2	19.2	20	20
------	------	----	----

The flare of the reaction to epinephrine also increases:

8	8.6	9.2	10
---	-----	-----	----

A confirmation of these increases is had in columns 22 and 23.

Summary.—The correlations of the level of the blood calcium are, therefore, with the following: blister time, blood sugar level, the resistance of the skin to electric current, the reaction to ice and the diameters of the wheal and flare of the reaction to epinephrine; and probably with the following: pulse rate, systolic blood pressure and pulse pressure, and CO₂ combining power.

POTASSIUM (COLUMN 5)

The average value of the blood potassium for the 100 men is 20.4. The fluctuations in the individual person's level of blood potassium are greater, as is well known, than those of the level of the calcium, changes of several milligrams per hundred cubic centimeters taking place during the course of the day. The normal range of values, too, is much greater, being from 13.4 to 28.8 mg. in our group.

Our four groups average:

16	18.2	20.4	25.7
(13.4-17.4)	(17.4-19)	(19-22.8)	(22.8-28.8)

Inflammatory Index.—The relation of the inflammatory index has already been mentioned.

CO₂ Combining Power.—With increasing potassium values, the CO₂ combining power appears to increase:

56.7	56.5	57.7	58.8
------	------	------	------

The confirmation in column 17 is, however, not striking.

Age.—The sequence is suggestive:

50	48	46	45
----	----	----	----

The expected confirmation in column 19 is, however, lacking.

Reaction to Epinephrine.—The pulse pressure shows a percentage increase with increasing amounts of potassium:

9.4	9.4	18.6	16.3
-----	-----	------	------

The pulse pressure \times the pulse rate shows a percentage progress as follows:

15.4	16.8	28.4	23.2
------	------	------	------

which is confirmed for the pulse rate in column 15.

Muscle Reaction.—The group averages are:

3	3.4	3.6	2.66
---	-----	-----	------

a rather irregular sequence, but the control (column 12) is somewhat clearer:

21.9	19.6	20.5	18.7
------	------	------	------

Reaction to Thyroxin.—The most convincing correlations are those with the reactions of the skin to intracutaneous injections of thyroxin and caffeine. The wheals average (in millimeters):

12.2	11.4	11.6	9.2
------	------	------	-----

This correlation is confirmed in column 26. The flares in the four groups average (in millimeters):

6.4	5.6	4.4	2.8
-----	-----	-----	-----

and this is confirmed in column 27.

Reaction to Caffein.—The wheals due to caffein show in similar relation:

20	20.4	18.6	11
----	------	------	----

confirmed in columns 28 and 29. The flares average:

2.8	4.8	3	1.6
-----	-----	---	-----

Summary.—Apart from the distinct relation to the inflammatory index, the potassium values influence the reactions to epinephrine and the reaction of the skin to thyroxin and caffein; their relation to the CO₂ combining power, the muscle reaction and age are less certain.

THE K/CA RATIO (COLUMN 6)

The average value of the K/Ca ratios of the 100 men is 2. The averages for the four groups are:

1.45	1.81	2.35	2.66
------	------	------	------

Blister Time; Inflammatory Index.—The relations to the blister time and the inflammatory index have been discussed.

Resistance of the Skin.—A striking association exists with the resistance of the skin to electric current, the averages for which, in this grouping, are:

0.65	0.48	0.34	0.35
------	------	------	------

i. e., the groups with the increased K/Ca ratio have diminished resistance.

Reactions to Epinephrine.—The pulse pressures in the four groups average (per cent):

7.5	10	8.5	14
-----	----	-----	----

The values of the pulse pressure \times pulse rate average (per cent):

14.6	14	17	24
------	----	----	----

This correlation is confirmed in columns 15 and 16.

Weight/Length Ratio.—The thinner persons have a lower K/Ca ratio:

205	219	217	222
-----	-----	-----	-----

Confirmation of this is had in column 20.

Cholesterol Level.—Those with low K/Ca ratio also appear to have less blood cholesterol:

215	220	218	229
-----	-----	-----	-----

This is confirmed in column 21.

Skin Reactions.—As might be expected from the potassium relations, the parallelism to the reactions of the skin to thyroxin and caffein is suggestive.

Summary.—The K/Ca ratio may, therefore, be regarded as of importance in connection with the blister time, the inflammatory index, the electrical resistance of the skin, the reactions to epinephrine, the weight/length ratio, the level of cholesterol and the reactions of the skin to thyroxin and caffein.

BLOOD SUGAR (COLUMN 7)¹⁶

The average of the blood sugar levels of the entire group is 71.

The four groups have the following averages:

60	68	74	82
----	----	----	----

Calcium Level.—The possible relation of the calcium level has been discussed.

Reactions to Epinephrine.—The most apparent correlation is with the reactions to epinephrine. The increase in pulse pressure for the groups is (per cent):

8.5	14	12	18
-----	----	----	----

and the "cardiac output" (per cent) is:

13	21	22	29
----	----	----	----

This correlation is confirmed in columns 15 and 16.

Weight/Length Ratio.—As the sugar increases, the weight also increases:

205	219	217	222
-----	-----	-----	-----

This is confirmed in column 20.

The Flares Caused by the Intracutaneous Injection of Epinephrine Hydrochloride.—The averages for the groups are (in millimeters):

7.6	8.4	8.4	9
-----	-----	-----	---

This correlation is confirmed in column 23.

16. The sugar values are for serum.

Summary.—The following correlated factors are, therefore, to be considered: The level of the blood calcium, the sensitivity to epinephrine, the weight/length ratio and the reaction of the skin to epinephrine.

ALBUMIN/GLOBULIN RATIO (COLUMN 8)

The average value of the albumin/globulin ratio for the entire group is 2. The averages for the four groups are:

1.1	1.6	2.08	3.3
-----	-----	------	-----

Blister Time.—It has been previously noted that increasing blister time is associated with an increased amount of globulin. This seems confirmed by the fact that the first group under consideration here with a ratio of 1.1 has a blister time of nine hours.

Muscle Reactivity.—A good correspondence is found:

2.9	2.8	3.1	4
-----	-----	-----	---

and this correspondence is confirmed in column 12.

Reactions of the Skin to Epinephrine and Thyroxin.—The amount of flare due to the epinephrine is apparently associated:

8	8.2	9	9.2
---	-----	---	-----

This association is confirmed in column 23.

The averages for the wheals caused by the intracutaneous injection of thyroxin are:

11	11.6	11	12.6
----	------	----	------

These seem related (confirmed in column 26), as also those for the flares caused by thyroxin and for the wheals caused by caffeine.

Summary.—An increased amount of globulin is, therefore, probably related to an increased blister time, to an increased muscle irritability and to the reactions of the skin to epinephrine, thyroxin and caffeine.

KROMAYER LAMP ERYTHEMA TIME (COLUMN 9)

For the 100 men, the average time of the appearance of the erythema from the time of application of the Kromayer lamp is 2 hours. The averages for the four groups are (hours):

1.24	1.58	1.95	3.3
(75 min.)	(96 min.)	(117 min.)	(200 min.)

Blister Time and Inflammatory Index.—The parallelism with the blister time and the inflammatory index has been discussed.

Calcium Level.—The apparent relation to calcium is:

10.3	10.1	9.9	9.7
------	------	-----	-----

but there is no confirmation in column 4.

CO₂ Combining Power.—The relation to the CO₂ combining power may be seen in the following averages:

55.8	55	58	58.8
------	----	----	------

This correlation is confirmed in column 17.

Wheal Caused by Epinephrine.—The averages are:

20.4	20.4	20.4	18.4
------	------	------	------

Only the group with the long latent period appears to have some relation to the smaller wheal, the confirmation of this being found in column 22.

Summary.—The associations of the time of the erythema due to application of the Kromayer lamp appear to be the following: the blister time, the inflammatory index, the CO₂ combining power and the diameter of the wheal caused by epinephrine.

BASAL METABOLIC RATE (COLUMN 10)

The average basal metabolic rate for the entire number is +8. The averages for the groups are:

-8.9	+2.2	+13.3	+28
------	------	-------	-----

Reaction to Ice.—The reaction to ice as shown in the following averages, clearly parallels the basal rate:

16.3	19.3	20	20.4
------	------	----	------

and the parallelism in column 18 is equally good.

Resistance of the Skin to Electric Current.—As the basal rate increases, the resistance of the skin to electric current appears to decrease, although the sequence is not perfect:

0.47	0.39	(0.62)	0.3
------	------	--------	-----

Weight/Length Ratio.—A correlation appears to exist with the weight/length ratio, the more slender persons having the higher rate:

221	219	216	207
-----	-----	-----	-----

This is confirmed in column 20.

Skin Reaction.—The wheal due to epinephrine diminishes with the increased metabolic rate:

19.2	20	18.8	15.2
------	----	------	------

This is confirmed in column 22.

Summary.—The basal metabolic rate, therefore, appears to be correlated with the electrical resistance of the skin, the reaction to ice, the weight/length ratio and the diameter of the wheal due to epinephrine.

RESISTANCE OF THE SKIN TO ELECTRIC CURRENT (COLUMN 11)

The average resistance for the 100 men is 0.46 megohms per square centimeter. The averages for the four groups are:

0.14	0.27	0.40	1.03
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Inflammatory Index, Calcium, K/Ca Ratio and Metabolic Rate.—The parallelisms here have been discussed.

Muscle Reaction.—A higher resistance of the skin appears to be associated with a lower threshold response of the muscle, the averages being:

3.6	3.5	2.5	2.7
-----	-----	-----	-----

This association is confirmed in column 12.

Weight/Length Ratio.—The thinner persons have a high resistance:

220	230	217	200
-----	-----	-----	-----

This is confirmed in column 20.

Skin Reaction.—The flare due to epinephrine increases with the resistance of the skin to electric current:

8.4	8.6	8.4	9.8
-----	-----	-----	-----

This is confirmed in column 23.

The flare caused by thyroxin averages:

3.4	5.2	5.2	5.6
-----	-----	-----	-----

The correlation is confirmed in column 27.

Summary.—The resistance of the skin to electric current has associations with the inflammatory index, the K/Ca ratio and the level of calcium, the metabolic rate, the muscle reaction, the weight/length ratio, the amount of flares due to epinephrine and thyroxin, and possibly the permeability of the capillaries.

MUSCLE REACTIVITY (COLUMN 12)

The average for the muscle reactivity of the whole number is 3.2 milliamperes. The averages for the four groups are:

1.7	2.3	3.66	6.1
-----	-----	------	-----

Albumin/Globulin Ratio and Skin Resistance.—The relations here have been discussed.

Pulse Rate.—The pulse rate diminishes as the muscle reactivity diminishes:

78	74	68	70
----	----	----	----

This relationship is checked in column 14.

CO₂ Combining Power.—One should anticipate a distinct decrease in the CO₂ combining power with decreasing reactivity. The results recorded in the table, however, indicate the opposite. The control is also irregular.

Weight/Length Ratio.—The weight/length ratio increases with the muscle reactivity:

207	221	228	224
-----	-----	-----	-----

This increase is confirmed in column 20.

Reaction to Caffein.—The wheal due to the intracutaneous injection of caffein increases in diameter with increase in muscle reactivity:

15.8	18.8	(17.4)	19.6
------	------	--------	------

The parallel increase is checked in column 28.

Summary.—In addition to the correlations with the albumin/globulin ratio and the skin resistance, correlations with the following seem possible: the pulse rate, the weight/length ratio and the diameter of the wheal due to caffein.

SYSTOLIC BLOOD PRESSURE (COLUMN 13)

The average blood pressure for the whole number is 124 systolic and 71 diastolic. The averages for the four groups are:

104	118	128	146
-----	-----	-----	-----

Diastolic Blood Pressure and Pulse Pressure.—Naturally the diastolic blood pressure corresponds:

62	70	72	76
----	----	----	----

as well as the pulse pressure:

42	58	56	68
----	----	----	----

Reaction to Epinephrine.—The pulse pressure, as well as the pulse pressure \times pulse rate, is distinctly associated with the systolic blood pressure, the averages being (per cent):

21	12	9.9	9.4
27	20	18	16

Age.—The age increases with the systolic pressure:

45	(43)	46	54
----	------	----	----

This correlation is checked in column 19.

Reaction to Caffein.—The flare diminishes:

7.6	3	2.2	3.8
-----	---	-----	-----

This is confirmed in column 29.

Summary.—The associations (apart from those with diastolic and pulse pressure) apparently are with the following: the reaction to epinephrine, the age and the radius of the flare due to the intracutaneous injection of caffein.

PULSE RATE (COLUMN 14)

The average pulse rate for the 100 men is 72.5. The averages for the four groups are:

60	69	76	86
----	----	----	----

Calcium Level and Muscle Reaction.—The relations here have been discussed.

Reaction to Epinephrine; CO₂ Combining Power.—The apparent correlations with the "cardiac output" following epinephrine injection and with the CO₂ combining power are not confirmed in columns 16 and 17.

Reaction to Caffein.—The averages for the wheal are:

18	(19.4)	17.8	16
----	--------	------	----

This relation is confirmed in column 28.

Summary.—The correlations appear to be with the following: the level of calcium, the muscle reaction, the reaction to caffein, and possibly with the CO₂ combining power and the reactions to epinephrine.

REACTIONS TO EPINEPHRINE: EFFECT ON PULSE PRESSURE
(COLUMN 15)

The average increase of the pulse pressures of the 100 men is +14.7 per cent during the hour following injection. The increase or decrease (per cent) for the four groups is:

—3.5	+6	+16	+36
------	----	-----	-----

Permeability of Capillaries, Potassium Level, K/Ca Ratio, Sugar and Systolic Blood Pressure.—The relations here have been discussed.

Pulse Pressure.—The persons with the greatest reaction to epinephrine are in the group who have the smallest pulse pressures before the injection:

54	56	50	42
----	----	----	----

There is no confirmation here because no results are arranged on the basis of pulse pressure.

Cardiac Output.—The correlation is such as might be expected.

Weight/Length Ratio.—The more slender men show the greater reaction to epinephrine:

225	216	215	197
-----	-----	-----	-----

This is partially confirmed in column 20.

Summary.—The chief correlations are, therefore, with the permeability of the capillaries, the potassium level, K/Ca ratio, the sugar level, the systolic blood pressure and the weight/length ratio.

REACTIONS TO EPINEPHRINE (COLUMN 16): "CARDIAC OUTPUT"
(PULSE PRESSURE × PULSE RATE)

The average increase of the "cardiac output" of the 100 men is 20.5 per cent. The increase (per cent) for the four groups following the injection of epinephrine hydrochloride is as follows:

—1.7	+19	+24	+42
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K/Ca Ratio, Sugar, Reaction to Epinephrine (Pulse Pressure).—The correlations here have been discussed.

CO₂ Combining Power.—The correlation with the CO₂ combining power is good:

57.4	57.8	57.9	59.5
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but the control (column 17) does not check.

Reactivity to Epinephrine.—The flares averaged (in millimeters):

8.6	8.6	9.2	9.6
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The control may be read in column 23.

Summary.—Only a few correlations can, therefore, be ascertained: these are with the K/Ca ratio, the sugar level and the diameter of the flare due to epinephrine, and, possibly, with the permeability of the capillaries and the CO₂ combining power.

CO₂ COMBINING POWER (COLUMN 17)

The average CO₂ combining power of the 100 men is 57.7. The averages for the four groups are:

53.5	56.5	58	62.3
------	------	----	------

Kromayer Lamp Erythema Time.—The correlations have been commented on previously.

Reaction to Ice.—The reaction time increases with the increase in CO₂ tension, the averages being as follows:

17	20	19	19
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The control (column 18) affords some support.

Weight/Length Ratio.—A distinct correlation exists here, the more slender men having a higher CO₂ combining power:

229	218	210	212
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Reaction to Thyroxin.—The amount of flare of the reaction to thyroxin seems related:

6.4	3.4	5.	4.4
-----	-----	----	-----

The confirmation appears in column 27.

Summary.—The apparent correlations are with the weight/length ratio, the reaction to ice, the Kromayer lamp erythema time and the amount of flare in the reaction to thyroxin.

ICE REACTION TIME (COLUMN 18)

For the 100 men, the average time of the reactions to ice is nineteen seconds. The averages for the four groups are (seconds):

9	15	20	32
---	----	----	----

Calcium, Basal Metabolic Rate, CO₂ Combining Power.—The correlations with these have been discussed.

Age.—The relation to age is obvious:

44	45	48	49
----	----	----	----

This relation is confirmed in column 19.

Skin Reactions.—A possible relation exists to the radius of the flare in the reaction to thyroxin and to the dimensions of both wheal and flare in the reactions to caffein. The averages for the former are:

5.8	5	5.4	2.6
-----	---	-----	-----

This is confirmed in column 27.

The averages for the wheal and the flare of the reaction to caffein are:

20.6	18.2	18.8	14
2.4	2.2	3.4	3

These correlations are confirmed in column 28 and column 29, respectively.

Summary.—The correlations are, therefore, with the age, the level of the calcium, the basal metabolic rate, the CO₂ tension, the radius of the flare of the reaction to thyroxin and the dimensions of both the wheal and the flare of the reactions to caffein.

AGE (COLUMN 19)

The average of the ages of the 100 men is 46.5. The averages for the four groups are:

30	42	51	65
----	----	----	----

Blister Time, Permeability of Capillaries, Inflammatory Index, Systolic Blood Pressure, Reaction to Ice.—The correlations here have been discussed.

Reaction to Caffein.—There is some indication that the diameter of the wheal increases with the age:

14.6	13.4	21	21.4
------	------	----	------

The confirmation of this is in column 29.

Summary.—The correlations are with the blister time, the permeability of the capillaries, the inflammatory index, the potassium level, the blood pressure, the reaction to ice and the reaction to caffein.

WEIGHT/LENGTH RATIO (COLUMN 20)

The average of the weight/length ratios of the 100 men is 217. The averages for the four groups are:

187	207	216	232
-----	-----	-----	-----

Permeability of Capillaries, K/Ca Ratio, Sugar Level, Basal Metabolic Rate, Skin Resistance, Muscle Reaction, Reactions to

Epinephrine and CO₂ Combining Power.—The correlations here have been commented on.

Cholesterol Level.—The averages for cholesterol show a relation (confirmed in column 21) as follows:

210	217	216	225
-----	-----	-----	-----

Skin Reactions.—The diameters of the wheals in the reactions to epinephrine average (in millimeters):

18.8	18.8	19.6	20
------	------	------	----

This correlation is confirmed in column 22.

The flares of the reactions to the intracutaneous injection of morphine average (in millimeters):

14.8	15	16.6	15.8
------	----	------	------

This parallel increase is confirmed in column 25.

Summary.—The correlations in this grouping are seemingly most extensive.

CHOLESTEROL (COLUMN 21)

The average of the cholesterol values for the entire number examined is 207. The average for the groups are:

181	219	202
-----	-----	-----

Only three groups were arranged because determinations of cholesterol were not made for the entire series.

Correlations.—The correlations are with the K/Ca ratio and the weight/length ratio. It appears that the pulse pressure also bears some relation, diminishing as the cholesterol increases. The correlations are, therefore, few.

REACTIONS TO EPINEPHRINE: THE WHEAL (COLUMN 22)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of epinephrine hydrochloride is 19.2 mm. The averages for the groups are:

16.8	17.6	20.4	22.
------	------	------	-----

Calcium Level, Basal Metabolic Rate, Weight/Length Ratio, Kromayer Lamp Reaction Time.—We have previously called attention to the possible correlations here.

Pulse Pressure.—The pulse pressure seemingly increases with the size of the wheal:

51	50	56	56
----	----	----	----

No check is possible, however.

Reaction to Caffein.—The averages of the diameters of the wheals indicate a relation (checked in column 28):

(18)	20.2	19.4	13.2
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Summary.—The correlations are, therefore, with the calcium level, the basal metabolic rate, the weight/length ratio, the Kromayer lamp erythema time and the reactions to caffeine.

REACTION TO EPINEPHRINE: THE FLARE (COLUMN 23)

The average of the radii of the flares in the reactions of the 100 men to epinephrine is 8.8 mm. The averages for the groups are:

5.8	8.8	10	11.6
-----	-----	----	------

Calcium, Sugar, Albumin/Globulin Ratio, Skin Resistance, Reaction to Epinephrine (Pulse Pressure \times Pulse Rate).—The correlations with these have been previously discussed.

Reactions to Morphine Flare.—The flares of the reactions to morphine show a parallel increase (checked in column 25):

13.2	15	16	16.6
------	----	----	------

Reactivity to Caffein.—The wheals in the reactions to caffein also show a relation (checked in column 28):

18	19.4	18.6	14.4
----	------	------	------

Summary.—The relations are, therefore, to the calcium level, the sugar level, the albumin/globulin ratio, the skin resistance, the reaction to epinephrine (pulse pressure \times pulse rate) and the reaction to morphine (flare) and to caffein (wheal).

REACTION TO MORPHINE: THE WHEAL (COLUMN 24)

The average of the diameters of the wheals in the reactions of the 100 men to intracutaneous injections of morphine is 12.4 mm. The averages for the four groups are:

9	10.6	11.8	14.
---	------	------	-----

No correlations are found.

REACTION TO MORPHINE: THE FLARE (COLUMN 25)

The average of the radii of the flares in the reactions of the 100 men to morphine is 15.6 mm. The averages for the groups are:

10	14.4	16.6	22
----	------	------	----

The correlation with the weight/length ratio has been referred to. The amount of flare in the reaction of the skin to epinephrine is apparently related:

7.8	8.8	9.6	10
-----	-----	-----	----

REACTION TO THYROXIN: THE WHEAL (COLUMN 26)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of thyroxin is 13.6 mm. The averages for the groups are:

7.6	10.4	12	14.6
-----	------	----	------

Inflammatory Index, Potassium, K/Ca Ratio, Albumin/Globulin Ratio.—The correlations here have been discussed.

Reaction to Thyroxin (Flare).—The averages for the flares are:

2.6	3.6	6.6	6.2
-----	-----	-----	-----

This may be checked in column 27.

Reaction to Caffein.—The averages for the wheals in the reactions to caffein are:

8.6	19	22.2	20.6
-----	----	------	------

for the flares:

1.2	2.4	2.8	4.2
-----	-----	-----	-----

These parallel increases may be checked in columns 28 and 29, respectively.

Summary.—The correlations, therefore, are with the inflammatory index, the potassium level, the K/Ca ratio, the albumin/globulin ratio, the amount of flare in the reaction to thyroxin and the reaction to caffein (wheal and flare).

REACTION TO THYROXIN: THE FLARE (COLUMN 27)

The average of the radii of the flares in the skin reactions of the 100 men to thyroxin is 4.8 mm. The averages for the four groups are:

0	4.6	8.6	10.6
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In this grouping, fifty-six men showed no reaction to the thyroxin. These fifty-six are represented by zero; the other three groups, consisting of 18, 19 and 19 men each, showed flares as set forth.

The averages for the wheals in the reactions to caffein (checked in column 28) are as follows:

16.3	15.	20.8	20.2
------	-----	------	------

for the flares:

0.8	4.6	2	5.8
-----	-----	---	-----

Correlations.—Previously discussed correlations include those with the potassium level, the K/Ca ratio, the resistance of the skin to electric current, the reaction to ice, the reaction to epinephrine (wheal) and the size of the wheal in the reaction to thyroxin. It is to be noted that the caffein reaction is closely related.

REACTION TO CAFFEIN: THE WHEAL (COLUMN 28)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of caffein is 17.6 mm. The averages for the four groups are:

7.6	15.2	21.6	25
-----	------	------	----

Correlations previously discussed include those with the potassium level, the K/Ca ratio, the reaction to ice, the albumin/globulin ratio, the muscle reaction, the pulse rate, the age and the reaction of the skin to epinephrine (wheal and flare) and to thyroxin (wheal and flare).

REACTION TO CAFFEIN: THE FLARE (COLUMN 29)

The average of the radii of the flares in the reactions of the 100 men to caffein is 2.75 mm. The averages for the groups are:

0 4 7.4 11

In this grouping, sixty-four men gave no flares. They are represented by the zero. The other three groups, consisting of twelve men each, gave flares averaging as set forth.

TABLE 2.—*The Relations of the Blister Time, the Inflammatory Index and the Kromayer Lamp Erythema Time to Mineral Balance and Other Factors*

	Blister Time, Increasing →	Inflammatory Index ←	Kromayer Lamp Erythema Time, Increasing →
Calcium level.....	→	(←)
Potassium level.....	←	→	←
K / Ca ratio.....	←	→	←
CO ₂	←	→
Muscle reaction.....	→
Albumin / globulin ratio.....	←	(←)
Basal metabolic rate.....	←	(→)
Vascular reaction to epinephrine.....	←	(←)	←
Skin reaction to epinephrine.....	←
Resistance of skin to electric current.....	←
Weight / length ratio.....	←	→	←

Correlations with the permeability of the capillaries, the systolic blood pressure, the reaction to ice, the age and the reaction to thyroxin (wheal and flare) have been previously discussed.

COMMENT

Blister Time, Inflammatory Index, Kromayer Lamp Erythema Time.—That the reactivity of the skin to cantharides, as estimated by the blister time, the inflammatory index and the reaction time to the Kromayer light, is closely associated with the mineral balance becomes apparent in table 2.

The agreement concerns chiefly the potassium level, the K/Ca ratio and the weight/length ratio. The blister time and the reaction time to the Kromayer light are, furthermore, in alinement with relation to the vascular reaction to epinephrine.

If one classifies the men examined on the basis of the vascular reaction to epinephrine, one must conclude that vagotonic (lessened or negative) reaction to epinephrine is associated with prolonged blister time and prolonged Kromayer lamp erythema time.

Permeability of the Capillaries, Inflammatory Index.—We turn next to another factor of the inflammatory index, permeability of the capillaries. In table 3 a comparison of this factor with mineral balance and other factors is made. The correlation with the reaction time to the Kromayer light falls away because there is no apparent direct relationship between this and permeability of the capillaries. Here it again becomes evident that the K/Ca ratio, the CO₂ combining power, the

TABLE 3.—*The Relations of Permeability of the Capillaries and Inflammatory Index to Mineral Balance and Other Factors*

	Permeability of Capillaries →	Inflammatory Index →
Calcium level.....	(?) →
Potassium level.....	→
K / Ca ratio.....	←	←
CO ₂	→	→
Muscle reaction.....
Albumin / globulin ratio.....	→	→
Basal metabolic rate.....	←
Age.....	←	←
Vascular reaction to epinephrine.....	→	(→)
Skin reaction to epinephrine.....
Skin resistance to electric current.....	→	→
Weight / length ratio.....	←	←
Reaction to thyroxin and caffeine (flares).....	→

albumin/globulin ratio, the age, the weight/length ratio and the resistance of the skin to electric current are related.

From tables 1 and 3, it is obvious that permeability of the capillaries of the skin, while related to the K/Ca ratio, appears to be less under the influence of the actual concentrations of these elements. There is a clear relation to age, to the vascular responsiveness to epinephrine, to the resistance of the skin to electric current and to the weight/length ratio.

Variations of the endocrine status, particularly as concerns thyroid activity, are probably chiefly concerned. The younger person has presumably greater secretory activity, greater permeability of the capil-

laries and a more marked sensitivity to epinephrine. The width of the flares in the skin reaction to thyroxin and caffein forms part of this picture.¹⁷

In table 4 the various factors that have been examined are grouped as they relate to skin reactivity. When one examines this table, a number of consistent correlations immediately stand out:

The increase in permeability of the capillaries proceeds with an increase in the inflammatory index and in the flares due to epinephrine, thyroxin, caffein and morphine (not shown in table).

Increase in the serum calcium is associated with (1) a prolonged reaction time to ice, but with a diminished reaction time to the Kromayer light; and (2) an increase in the size of the wheal and the flare due to epinephrine, but a decrease in the size of the wheal due to thyroxin. These contrary reactions to epinephrine and thyroxin have been observed previously.¹⁷

Increase in potassium proceeds with (1) an increase in the inflammatory index, but is associated with a prolongation of the erythemas due to the application of the Kromayer light and ice; and (2) a decrease in the size of the wheals and flares due to thyroxin and caffein.

Increase in the K/Ca ratio proceeds with (1) an increase in the inflammatory index, but a delay in the reaction to ice, and (2) an increase in the reactions to thyroxin and caffein as the K/Ca ratio is lowered.

Increase in the CO₂ combining power of the serum (in the direction of an alkalosis) accompanies (1) increase in the inflammatory index and increase in the time of erythema due to the applications of the Kromayer light and ice; and (2) increase in the wheal due to epinephrine and decrease in the wheal due to thyroxin.

Increase in the basal metabolic rate accompanies (1) increase in the inflammatory index, shortening of the reaction to the Kromayer light and prolongation of the reaction to ice, and (2) decrease in the wheal and flare due to epinephrine.

As the weight/length ratio increases (in heavier persons), the wheal due to epinephrine increases in size, while the wheal due to thyroxin tends to diminish.

Table 5 presents the blood chemistry and its correlations with the weight/length ratio and other factors. When one examines this table on the basis of the weight/length ratio, one finds that as weight increases, four reactions may be grouped: 1. Permeability of the capillaries diminishes. 2. Potassium increases. 3. The K/Ca ratio increases. 4. The CO₂ combining power diminishes.

17. Petersen, W. F., and Levinson, S. A.: IV. The Patient with Exophthalmos and the Nervous Patient, *Arch. Path.* (p. 267, this issue).

TABLE 4.—*The Relations of the Various Factors Examined to Skin Reactions*

	Inflammatory Index	Reaction to Kromayer Light	Reaction to Ice	Skin Reactions					
				Epinephrine, Wheal	Epinephrine, Flare	Thyroxin, Wheal	Thyroxin, Flare	Caffein, Wheal	Caffein, Flare
Blister time.....	..	+	+	+
Permeability of capillaries.....	+	+	..	+	..	+
Inflammatory index.....		+	+
Calcium level.....	..	+			+	+
Potassium level.....	+	..	+	+	+	+	+
K / Ca ratio.....	+	..	+	+	+	+	+
CO ₂ combining power.....	+	+	+	+	..	+	+
Sugar level.....	+	+	+
Albumin / globulin ratio.....	+	+	+	+	+	..
Vascular reaction to epinephrine.....	+	+
Skin resistance to electric current.....	+	..	+	..	+
Basal metabolic rate.....	+	+	+	+	+
Muscle reaction.....	..	+	+	..	+	+	..
Blood pressure.....	+	..	+	+
Age.....	+	..	+	+	..
Weight / length ratio.....	+	..	+	+	+	..
Reaction to ice.....		+	+	+	+
Reaction to Kromayer light.....	+		..	+

TABLE 5.—*The Blood Chemistry and Its Correlations with the Weight/Length Ratio and Other Factors*

	Weight / Length Ratio	Vascular Reaction to Epinephrine	Sugar Level	Muscle Reaction	Pulse Rate	Blood Pressure	Reaction to Epinephrine, Wheal	Reaction to Epinephrine, Flare	Reaction to Thyroxin, Wheal	Reaction to Thyroxin, Flare
Inflammatory index.....	+	..
Permeability of capillaries.....	+	+	+	+	+	+
Calcium level.....	+	..	+?	..	+	+	+	..
Potassium level.....	+	+	..	+	+	+
K / Ca ratio.....	+	+	..	+	+	+
CO ₂ combining power.....	+	+?	..	+	..	+	+
Albumin / globulin ratio.....	+	+	+	+	+	+
Basal metabolic rate.....	+	+	+
Skin resistance.....	+	+	+
Muscle reaction.....	+		+	+	..	+
Sugar level.....	+	+		+	+
Age.....	+
Weight / length ratio.....		+	+	+	..	+	+
Pulse rate.....	+		+
Blood pressure.....	..	+	+
Reaction to ice.....	+	..	+	+
Kromayer lamp erythema time....	+
Vascular reaction to epinephrine..	+		+	..	+	+	..	+?
Reaction to epinephrine, wheal....	+	+	..
Reaction to epinephrine, flare.....	+		+	+
Reaction to thyroxin, wheal.....		+
Reaction to thyroxin, flare.....	+	+	..	+	

This group of chemical correlations is distinctly related to the wheal and flare due to thyroxin, both of which diminish with increasing weight.

With the increase in weight, the second group of reactions is to be studied: 1. The basal metabolic rate diminishes. 2. The resistance of the skin to electric current increases. 3. The muscle reactivity diminishes. 4. The sugar increases.

This second group of reactions is not so closely related to the K/Ca ratio (muscle reaction is related to the potassium level, and the sugar to the calcium), but it shows a distinct correlation with the skin reactions to epinephrine. The wheal of the latter increases with increasing weight, and with lowered metabolic rate; the flare diminishes.

If one wishes to use the term sympathetictonic or vagotonic, one can say that the heavy group is the parasympathetic group, and the thin group the sympathetictonic. We do not, however, believe that these terms are justifiable or helpful, because there are too many divergent autonomic reactions. (Table 6.)

TABLE 6.—*The Relation to Weight*

Heavy Persons		Thin Persons
Low	Permeability of the capillaries.....	High
High	Potassium.....	Low
High	K / Ca ratio.....	Low
Low	CO ₂	High
Low	Basal metabolic rate.....	High
Low	Skin resistance to electric current.....	High
Low	Muscle reactivity to electric current.....	High
Low	Reaction to epinephrine (pulse pressure).....	High
Increased	Reaction to epinephrine, wheal.....	Diminished
Increased	Reaction to epinephrine, flare.....	Diminished
Diminished	Reaction to thyroxin, wheal.....	Increased
Diminished	Reaction to thyroxin, flare.....	Increased
Increased	Cholesterol.....	Decreased

The age of persons plays relatively little rôle in the reactivities that we have studied. The blood pressure is, of course, increased and the inflammatory index is lowered, as is the permeability of the capillaries. The reaction to ice, too, is somewhat delayed in old age.

EXPLANATION OF TERMS USED

Blister Time.—The time in hours for the formation of a blister on the forearm following the application of a cantharides plaster.

Permeability of Capillaries.—The ratio of the protein in the blister to the protein in the capillary blood.

Albumin/Globulin Ratio.—Method of Naegle.

Krohmayr Erythema Time.—The time in hours for the first appearance of erythema following a thirty-second exposure of the forearm to the Krohmayr lamp.

Skin Resistance.—The resistance of the skin of the forearm to the passage of a direct current of electricity.

Muscle Reaction.—Muscle reaction (CCC).

Epinephrine Reaction.—The average percentage increase or decrease from the preinjection level of the pulse pressure for one hour after the injection.

Epinephrine Reaction.—The average percentage increase or decrease from the preinjection level of the pulse pressure times pulse rate for one hour after the injection.

Ice Reaction.—The time in seconds for the appearance of an erythema following a transient application of ice to the chest wall.

Weight/Length Ratio.—The weight in pounds divided by the length in inches.

Intracutaneous Reactions to Pharmacologic Substances.—The size of the wheal and of the flare (in mm.) at the site of the intracutaneous injection of epinephrine hydrochloride 1:1,000,000, 1:100,000, 1:10,000 and 1:1,000; morphine 1:10,000,000 and 1:1,000,000; thyroxin 1:10,000 and caffeine 1:100.

II. THE CLINICAL STATUS OF THE GROUP OF ONE HUNDRED "NORMAL" MEN

In the first part of the study, we presented a table of possible correlations of certain reactions of the skin (the blister time, the reaction time to the Kromayer light, the reaction time to ice, the resistance of the skin to electric current, the reactions to intracutaneous injections of pharmacologic substances, etc.) with the blood chemistry.

In the present analysis of this material, we proceed to a grouping of the men into clinical subdivisions, based on the physical observations and on the results of the urinalyses, the examinations of the blood pressures, the Wassermann tests, the roentgenologic interpretations, the microscopic examinations of the capillaries of the skin, etc.

In arranging the individual results of the examinations of these men, we first present table 1, which classifies the men as follows: a normal group of 20 men (column 3); a group of 9 proved by the x-rays to have active tuberculosis (column 4); a group of 17 with healed parenchymal tuberculosis, as evidenced by the x-rays (column 5); a group of 4 with syphilis (column 6); a group of 40 with cardiovascular renal disease, which has been subdivided to include those with arteriosclerosis, as shown by the x-rays (column 7), those with probable myocarditis, as shown by the x-rays (column 8), those with an increased range of blood pressure (column 9), those with a normal range of blood pressure (column 10), those with a low range of blood pressure (column 11), those with changes in the urine—casts or albumin (column 12) and those with alterations of the capillaries of the skin—granulation, tortuosity, slowing, etc. (column 13); a sensitized group of 2 (column 15); a "nervous" group of 4 (column 16), and a group of 4 with miscellaneous conditions, making a total of 100 men.

The following tables have been prepared: Table 2 contains the results of the examinations of the normal men; table 3, of men with roentgen evidence of healed tuberculosis, and table 4, of men with roentgen evidence of active tuberculosis.

The cardiovascular renal material has been recorded in the following way: in table 5, the results of the examinations of men with increased blood pressure, but without urinary changes; in table 6, of men with increased blood pressure with urinary changes; in table 7, of men with normal blood pressure and normal urine, but with x-ray evidence of arteriosclerosis or myocarditis; in table 8, of men with normal blood pressure, but with urinary changes; in table 9, of men with blood pressure under 110 (including the syphilitic group, normal men and men with roentgenologic evidence of healed tuberculosis), and in table 10, of men with low blood pressure, but with urinary changes.

The averages for these groups have been brought together in table 11.

TABLE 1.—Classification of One Hundred So-Called Normal Men on the Basis of the Results of Physical Examinations

Cardiovascular Renal																
Serial Number	Individual Number	Normal Persons	Tuber- culosis, Shown by Roentgen- ogram		Syphilis	Arteriosclerosis of Large Vessels (X-Ray)	Myocarditis (X-Ray)	Blood Pressure			Changes in Urine (Casts or Albumin)	Changes in Skin Capillaries	Cardiovascular Renal	Sensitized	Nervous	Miscellaneous
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	3	1
2	4	1
3	8	1
4	10	1
5	13	1
6	14
7	15	1
8	17	1
9	18	1
10	20	..	1
11	21	+	1
12	23	1
13	24	1
14	25	..	1
15	26	1
16	28	1
17	29	1
18	30	+	1
19	32	1
20	34	+	1
21	35	1
22	36	1	+
23	37	1
24	39	+	1
25	40	+	1
26	41	1
27	42	1
28	43	1
29	44	1
30	45	1
31	46	+	1 Inanition
32	47	1
33	48	+	1
34	49	1
35	50	1
36	52	1
37	53	1
38	54	1	+
39	55	+	1
40	56	..	1	+
41	59	1
42	61	1
43	62	1
44	63	+	..	+	1
45	64	1
46	65	1
47	66	+
48	67	1
49	68	1	Dwarf
50	70	1
51	71	1
52	72	1	1
53	73	1
54	74	1
55	75	+	1
56	76	+	1
57	77	1
58	78	1
59	79	+	..	+	1	Ulcer
60	80	+	..	1	..
61	81	1
62	82	1
63	83	1
64	84	1
65	85	1	Elevated tempera- ture (cause un- known)

TABLE 1.—Classification of One Hundred So-Called Normal Men on the Basis of the Results of Physical Examinations—Continued

Cardiovascular Renal																
Serial Number	Individual Number	Normal Persons	Tuberculosis, Shown by Roentgenogram		Syphilis	Arteriosclerosis of Large Vessels (X-Ray)	Myocarditis (X-Ray)	Blood Pressure			Changes in Urine (Casts or Albumin)	Changes in Skin Capillaries	Cardiovascular Renal	Sensitized	Nervous	Miscellaneous
1	2	3	4 Active	5 Healed				9 High	10 Normal	11 Low						
66	86		+	1	..
67	87	1	+
68	88		1
69	89			1	+
70	90		1	..
71	91		+	+	+	1
72	92		+	1	..
73	93		+	..	+	1	+
74	94	1
75	95		..	1
76	96		+	..	+	1
77	97	1	+
78	98		+	+	1
79	99		..	1
80	100		..	1
81	101		..	+	+	..	1
82	102		1
83	103		+	+	..	+	1
84	104		1	+	..	+	+
85	105		..	1	+
86	106		+	+	1
87	107		+	+	1
88	108		1	+	+	+
89	110		..	1	+
90	111		..	+	..	+	+	1
91	112		+	1
92	113		..	+	+	1
93	114		1	+	..	+	+	..	+
94	115		..	+	+	+	..	1
95	122	1	+
96	127		..	+	+	..	+	..	1
97	128		..	+	..	+	+	..	+	+	1
98	129		1	+	+	+	1
99	130		+	+	+	1
100	134		+	..	+	..	+	1	(Aneurysm)
		20	9	17	4	3	37	2	4	4

COMMENT

The Normal Group.—In the normal group, there have been included men whose blood pressure is under 140, with no urinary changes, no roentgen evidence of tuberculosis and no alterations of the capillaries of the skin, with negative Wassermann reactions and without history of sensitization.

Even with such criteria, it is to be expected that certain ones may be abnormal in the sense that chronic pathologic conditions of the organs, either anatomic or functional, may exist, but need not be clinically apparent in one examination. Thus, a number of deviations are observed in the course of the examinations.

Blister Time: The blister time is shortened only in patient 122, a young medical instructor, apparently normal, who gives a history of

TABLE 2.—The Results of the Examinations of

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure \times Pulse Rate, per Cent
														Systolic	Diastolic			
4	6	62	9.5	11.8	21.2	1.8	94.3	...	8.28	2	+12	0.34	...	114	90	80	21	45.5
122	4	68	17	10.6	19.2	1.81	50	1.8	8.06	?	-7	0.27	2.4	102	50	68	-3	6
29	6.5	70	10.7	10	23.9	2.39	76	1	8.28	3.25	+3.5	0.37	1.1	134	88	70	+24	+24
35	8	54	6.7	8.7	25.2	2.9	79	2	8.28	1.25	+12.3	0.38	2.2	108	78	62	+53	+47
41	6	55	9.1	9.8	21.2	2.16	70	1	8.49	1.25	+15	0.26	3.2	110	74	64	+25	+33
43	6.25	60	9.7	9.2	17.4	1.89	67	1	7.63	1.75	-4.4	0.27	3.5	90	50	74	+18	+40
44	8	56	7	10	17.6	1.76	90	2	8.49	1.75	-1.2	0.36	3	120	68	60	+7	+22
50	8	71	8.8	11.4	27.4	2.4	...	2.3	8.28	3	+21	0.48	5	128	70	67	+12	+20
64	6.5	66	10	9	16.6	1.84	52	3.5	7.41	3	+23	0.22	5	113	59	64	+15	+18
72	6	69	11.5	10.8	18.7	1.73	72	2.8	7.73	2	+15.9	0.27	3.6	114	76	54	+23	+46
78	7	86	12	8.4	18.8	2.23	67	1.5	8.49	3.25	-6.2	0.62	1	122	70	74	+11	+20
83	9	51	5.6	8.2	19	2.31	68	1.5	7.73	1.5	-7	0.16	4	118	64	58	+9.0	+9
87	6	56	9.3	8.4	19.5	2.32	94	2.3	7.55	1.5	+18	0.42	4	102	58	69	+40	+53
97	6	54	9	8.4	20.9	2.37	60	1.4	7.85	1.75	+25	0.22	4.5	100	63	68	+20	+30
17	8	66	8.2	12.7	18.2	1.43	61.5	5	8.72	1.5	-11	0.22	6	130	70	66	0	0
53	8	62	7.7	...	22.8	...	77	3	8.06	1.5	+31.8	0.35	6.7	125	73	80	+32	+32
59	6	52	8.6	9.6	18.8	1.95	85	5	7.85	1.5	-6.5	0.16	4	116	69	74	+2	+8
8	7	75	10.7	10.5	21	2	73	2.12	8.06	1.15	-8	...	2.2	120	86	64	+90	+120
37	9	56	6.2	10	22.6	2.26	75	1.4	7.85	1.5	-24	0.34	3	116	70	84	-8	-6
94	6	53	8.8	8.4	17.5	2.08	75	1.7	7.85	1.45	-1.8	0.43	...	134	78	53	+20	+50
	6.8	62	9.3	9.7	26.3	2.1	72.8	2.22	8.04	1.83	+5	0.33	3.7	116	70	68	+19.6	+28.6

TABLE 3.—The Results of the Examinations of the Men who Were

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure \times Pulse Rate, per Cent
														Systolic	Diastolic			
95	6	59	9.8	7.8	18.8	2.41	77	2.3	8.5	1.85	+26	0.39	1.6	110	66	68	+9	+17
3	6.5	67	11.1	11.1	16.3	1.47	73.3	1.86	7.41	1.5	-6.5	0.33	...	114	65	76	+8	+26
13	8	64	8	9.6	23.8	2.48	78	4	7.7	2.5	-22	0.89	2.7	132	84	72	+24	+37
15	9	68	7.5	12.1	18.8	1.55	70.4	4	7.96	1.5	-4.9	0.19	6	128	68	60	+13	+20
21	6	67	11.1	13.1	28.6	2.19	85	...	7.87	1.75	+10.9	0.42	2	102	58	82	+25	+40
24	6	70	11.6	11.7	24.8	2.12	81	...	7.20	2	+1	0.19	2	110	58	78	+50	+62
52	8	61	7.6	10.4	20.9	2	66	4	7.85	1.5	+0.5	0.44	1	110	61	75	0	+4
100	6	53	9	21.5	2.38	72	1.2	7.85	1	...	+1.6	0.11	3.8	128	58	76	+8	+13
110	7.5	64	7.2	12.1	16.3	1.34	61	2.5	7.20	4	+48	0.00	2	114	60	86	-4	-4
68	7	78	11	8.8	17.1	1.94	68	2.3	8.66	1.5	+25.8	0.53	5	138	76	89	+31	+36
89	6	52	8.6	9.2	16.7	1.81	75	2	7.51	1.25	+25	0.16	1.6	100	60	73	0	+2
99	9	77	8.1	9.5	17.9	1.86	71	4	7.85	4.5	-3	0.14	4.2	116	78	70	+12	+24
105	9	62	7	9	17.1	1.81	52	1.6	7.63	2.5	+31.6	0.08	...	108	70	82	+26	+26
18	8	70	8.7	14.5	21.2	1.46	70.2	1.8	8.30	3.25	+4.2	1.00	2	120	80	88	10	...
28	6	64	10.6	11	24.1	2.19	72	1.4	7.63	1.75	+24.5	0.08	4	118	76	66	+21	+32
10	6	62	13.3	10.1	24.6	2.4	74	2.12	8.70	2.5	-12	0.42	3.6	120	70	70	0	0
47	5	64	12.8	10.4	26.2	2.51	72	1.5	8.38	1.45	+34	0.13	5	136	64	70	-5	+10
	7.3	64.8	9.6	10.5	20.8	1.98	71.6	2.43	7.88	2.15	+8	0.36	2.97	117	67	75	13.4	20

the Men Who Were Grouped as "Normal"

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
64	Sthenic	—	+	Normal	..	40	237	...	22.8	10.6	16	17	10.2	0	10.2	0
56.8	Asthenic	Normal	5	33	189	200	20	7.8	10	6.6	12	9	21.2	0
60.1	Sthenic	..	+	Normal	15	43	214	...	26.8	9.4	14	12.2	7.2	0	5	0
57.6	Sthenic	..	+	Normal	20	44	203	...	22.8	11	14.8	20.4	9.2	0	5.2	0
58.6	Asthenic	..	0	Normal	7	40	216	...	24	7.2	13.8	18.8	6.2	0	5.8	0
60.1	Asthenic	..	0	Decreased in quantity	7	45	231	...	22	7.4	11.2	20.6	10	0	11	0
57.1	Sthenic	..	0	Normal	20	48	244	...	19.6	9.4	12.8	15	10.2	3.8	15	4.4
64.9	Normal	15	20	237	...	21.8	10.6	9.8	15.4	10.4	10	14	0
55	Sthenic	Normal	7	31	208	180	20	10.6	13	15	12.2	10.8	16.2	0
60.6	Sthenic	..	+	Normal	20	42	230	185	18	12.2	15.6	17.8	15.4	6.6	20.2	15.4
62.6	Asthenic	Normal	10	33	203	238	19.6	12	9.4	20.4	12.4	6.2	20.2	10
53.1	Sthenic	Normal	20	43	258	196	17.2	9.2	9.2	20.8	13.4	11	21.4	7.4
55.4	Sthenic	Normal	18	46	200	222	16	8.8	10	12.4	12	5.4	25.4	10.2
57.2	Sthenic	..	+	Slight dilatation	20	53	230	245	19.2	9	8.8	16.4	12	9	33	0
59.1	Normal	..	0	Normal	20	28	216	...	22.8	10.2	12.4	7	20.6	10.4	30.4	2.6
53.9	Sthenic	Normal	10	39	231	...	17.2	11.8	10.4	20.4	12.2	11.2	23	6
56.6	Sthenic	Normal	10	37	252	...	23.6	7.2	9.2	21.4	15.6	8	23.4	6
56.1	Asthenic	..	+	17	38	200	...	20.4	9.8	13.2	13.4	14.4	0	19	0
52	Sthenic	..	+	Normal	20	45	254	...	22.8	7	10.2	15.2	6	0	8.4	0
51.5	Sthenic	Normal	15	57	236	303	20	6	11.2	14	11.2	7.8	30.6	0
57.6					14.5	40.2	224	222	21	9.36	11.7	16.3	11.6	5.45	17.9	3

Grouped as Having Roentgenographic Evidence of Healed Tuberculosis

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
61.6	Sthenic	Healed	..	Normal	10	54	222	318	23.6	6.4	10.2	12.6	12	6.2	26.2	..
...	Healed	..	Normal	14	25	224	213	19.4	12.2	12.4	18.2	6.4	...	4.8	..
68.6	Asthenic	Healed	..	Normal	15	53	223	185	13.2	6.8	12.4	11.2	22.6	9.2	25.6	..
67.6	Sthenic	Healed	38	60	210	...	23.2	12.6	11.2	12.4	11.6	12	12.4	10
57.4	Sthenic	Healed	0	Normal	28	54	233	...	17.2	8.2	10.6	17.8	9.2	3.2	7.2	4
53.7	Sthenic	Healed	+	Normal	20	30	219	...	16.8	12	9	27.2	6.6	...	7.2	...
52.9	Sthenic	Healed	..	Normal	15	36	213	...	17.6	10	12.8	19.2	11.2	12.4	20	7.8
58.3	Sthenic	Healed	..	Normal	5	45	241	206	18.8	8.6	11.4	10.6	12	9.2	27.6	..
57.2	Asthenic	Healed	..	Decreased	30	62	190	222	21.8	4.2	9.6	14.6	12	9.4	18.2	..
51.1	Asthenic	Healed	..	Normal	10	35	217	238	18	9.6	12.4	10.2	12	11	22.4	1
56.3	Asthenic	Healed	..	Normal	16	41	204	222	20.8	9.8	9.2	20	10.2	...	20.4	..
57.4	Sthenic	Healed	..	Normal	11	40	228	230	20.4	7	12.2	11.2	12.2	9.2	29.4	..
64.4	Asthenic	Healed	..	Normal	15	50	194	238	19.6	5.6	9.2	16	12	10.4	27.2	..
58.4	Asthenic	Healed	..	Normal	10	31	200	6.6	22.6
66	Asthenic	Healed	+	Normal	25	43	200	...	20	12.2	10.8	15.2	7.4	...	7.2	..
60.4	Sthenic	Healed	0	Normal	7	40	230	...	20	8.4	12.6	14.6	9	7.2	12.2	..
56.4	Sthenic	Healed	+	Normal	15	38	200	...	22.6	5.2	14.2	10.8	9	6
57.9					16.5	43.6	218	233	19.2	8.66	11	15.5	11	6.2	17	1.5

TABLE 4.—The Results of the Examinations of the Men Grouped

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure X Pulse Rate, per Cent
20	6	64	10.6	11.4	17.4	1.53	85	1.70	8.28	1.5	+20.4	0.25	5	..	130	76	80	+13	+28
25	6	57	9.5	11.1	28.8	2.60	67	0.43	8.50	1.75	+2	0.24	1.2	..	140	80	86	+35	+44
56	6	61	10	9.8	28.6	2.52	65	1.8	9.13	2.15	+17.9	0.32	1	..	124	88	79	+14	+32
104	9	54	6	7.4	22.9	3.09	55	1.2	7.51	1.75	+27.5	0.08	1.2	..	176	100	84	+11	+11
114	8.5	64	6	8	19.2	2.4	75	2.3	8.06	2.25	+11.2	0.12	4	Albunin, blood	174	60	48	+6	+60
129	15	52	3.5	8.9	19	2.13	83	1.3	7.85	2.5	+28	0.22	2.2	..	116	60	92	10	13
108	8	63	8	10.4	15.3	1.47	63	1	7.85	1.75	+17	0.44	0.6	..	94	52	71	+9	+29
102	11	64	5.8	10.6	17.3	1.63	62	0.82	7.95	1.5	+22	0.20	2.4	..	114	60	96	+11	+5
88	7.25	58	8	9.4	13.1	1.4	79	2	7.63	2	0.68	2.5	..	128	76	76	-10	0
	8.4	59	7.5	9.6	20.1	2.08	70	1.4	8.08	1.9	18.2	0.28	2.2	..	133	73	78	+11	+23

TABLE 5.—The Results of the Examinations of the Men in the Cardiovascular

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure X Pulse Rate, per Cent
46	6	59	10	13.8	17.4	1.24	61	2.3	7.63	1.15	+13	1.7	2	140	82	70	+15	+37
21	7	62	9	10.2	25.6	2.51	72	4	8.06	1.75	+4.3	0.74	3.9	140	80	72	0	-5
32	6	60	10	9.5	26.1	2.75	76	2.3	8.80	1.75	+22	1.18	7.4	144	86	74	+22	+30
45	6	54	9	11.2	16.6	1.48	77	1.5	7.73	0.75	+20	0.28	7.4	162	114	84	-3	+8
79	15	86	5.7	11.2	20	1.78	67	1	8.78	4	-15.2	0.71	7.7	140	80	60	+8	+10
81	6	59	10	8.4	25.8	3.07	63	1.7	8.49	1.5	+35	0.10	2.3	144	54	76	+4	+4
75	9	60	6.6	10.8	19.2	1.78	75	1.6	9.23	3	+2.5	1.3	5	146	80	77	-9	-15
82	6	58	9.6	11.4	17.2	1.5	58	2	7.41	1.5	+7	0.20	5.7	170	100	61	+31	+37
30	6	55	9.1	10.3	24	2.33	76	7.07	1.5	-5.9	1.05	1.8	150	72	85	0	-10
96	8.25	57	7	8.2	17	2.02	77	1.8	7.26	1.75	+31	0.11	2.6	140	85	68	+25	+28
	7.5	61	8.6	10.47	20.8	2	70.2	1.82	8.04	1.86	11.4	0.7	4.6	147	83	73	9.3	14.1

as Having Roentgenographic Evidence of Active Tuberculosis

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
62.3	..	Asthenic	++++	0	Normal	10-20	42	226	...	24.2	6.6	12.4	15.4	10	2.6	9	0
59.8	..	Asthenic	++++	0	Normal	20	35	183	...	21.4	12.2	8.2	17.8	9	15.2	10	6.2
56.5	..	Sthenic	++++	..	Normal	15	44	247	...	17.2	5.8	10.8	22.4	14	7	21.4	7.2
57.2	+	Dilatation of aorta, arteriosclerosis	++++	..	Normal	25	76	235	230	20.8	6.2	10.8	10	12	0	15.2	0
60.6	..	Sthenic	Left upper bronchus +	+	Normal	25	79	235	208	20	7.2	10.2	10.2	12	9	22.2	0
61.1	..	Sthenic	+ Hilum bronchi	+	Granulations	17	66	247	238	18.4	7	10.6	9.6	12.2	0	13.2	0
54.1	..	Asthenic	+	..	Slight granulations	18	67	196	139	18	2.4	10.2	11	14.8	13.2	28.4	3.4
60.9	+	Asthenic	+	+	Normal	40	65	170	208	23.2	7.4	10.8	15	12.2	0	18.2	7
58.1	..	Asthenic	+++	..	Normal	15	55	203	230	18.4	11	11.6	20	12.4	12	27.6	0
58.8						21	58.7	215	208	20	7.2	10.6	14.6	12	6.4	18	2.6

Renal Group Having Increased Blood Pressure but No Urinary Changes

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
56.2	..	Asthenic	..	+	Sluggish, empty	15	29	168	...	21.2	13.2	15.0	16.2	12.2	11.2	25.2	9.2
62.9	..	Asthenic	Healed	0	Dilated, in granulations	25	56	200	...	23.2	12.6	8.8	13.2	7.2	2.6	5.2	...
54.1	..	Sthenic	..	0	Normal	25	26	190	...	23.6	11.2	11	21.4	9.8	...	8.4	...
54.3	..	Sthenic, myocarditis	..	0	Normal	20	40	317	...	20.4	9.8	14.2	21.4	16.4	12	20	4.8
57	+	Arterio-sclerosis	Healed	..	Normal	20	58	220	230	19.2	9.4	10.2	17.8	8.2	12.2	30.6	5
57	..	Myocarditis	..	+	Normal	45	68	209	222	14	6.2	10.2	15	10	...	16.4	9.6
61.6	..	Sthenic	Healed	+	Normal	10	54	243	278	20.4	10.2	18	15.2	10	...	23.4	8
58.8	..	Sthenic	..	1800	Slightly tortuous	25	66	208	190	21.2	7	14.2	14.2	11	...	27.6	9
62	+	Arterio-sclerosis	..	0	Normal	15	42	175	...	20	8.8	8.2	16	7.2	...	7.2	...
53.4	..	Arterio-sclerosis	..	+	Normal	40	70	245	167	18	8.2	11.4	15.4	12.4	...	28.4	...
57.7						24	50.9	217.5	217	20.1	9.72	12	16.6	10.4	3.8	19.2	4.6

TABLE 6.—The Results of the Examinations of the Men in the Cardiovascular

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure \times Pulse Rate, per Cent	
61	6	10	11.6	7.6	17.9	2.35	72	3.5	7.41	1.75	+ 0.9	0.28	7.4	+	142	82	64	+ 8	+17	
70	10.5	74	7	11.4	16.6	1.45	67	1.9	8.65	1.25	+23	0.39	4	++	148	50	76	- 6	+ 2	
84	11	71	6.4	10	17.8	1.78	67	1	7.85	1.5	- 5	0.28	2.8	+	140	78	80	+ 0	+ 3	
115	8	46	5.7	7.8	15.2	1.95	60	0.66	8.28	1.65	+15	0.28	2	+	Albumin, sugar + Casts	148	84	84	- 4	- 4
134	15	60	4	9.9	15.4	1.56	71	1.4	7.85	1.35	- 4	0.7	...		146	86	78	0	+ 5	
	10.1	64	7	9.34	16.6	1.82	67	1.7	8	1.5	- 6	0.38	4		145	76	76	0	+ 4.6	

TABLE 7.—The Results of the Examination of the Men in the Cardiovascular Renal Group with Normal

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure			Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure \times Pulse Rate, per Cent
														Systolic	Diastolic	Pulse Rate		
42	7.25	47	6.5	11.4	17.8	1.56	71	1	7.63	2	+ 6.8	0.15	4.5	136	70	86	+ 0	+19
113	6.5	60	9.2	10.2	18.6	1.82	66	1.5	7.41	1.75	- 6.2	0.34	2.2	136	72	60	+ 8	+ 8
71	6	70	11.6	8.8	17.5	2	73	2.3	8.5	1.1	+ 7.4	0.36	2.4	114	70	88	+18	+18
93	6	50	8.3	7.6	24.5	3.2	70	1.4	8.59	1.45	0	0.25	2.4	114	71	86	+19	+19
103	6	52	8.6	9.2	17.3	1.88	57	1.5	7.73	1.75	+ 2	0.39	1.4	126	70	76	- 1	+ 6
106	6	71	12	11.2	19	1.69	65	1.7	8.06	1.45	- 6	0.63	2.2	120	80	84	- 5	- 1
107	9	58	6.4	8	18.4	2.3	60	1.5	8.06	4.75	- 6.5	0.33	2.8	134	72	72	- 1	+ 2
111	6	57	9.5	11.8	18.3	1.5	75	1.5	8.28	1.15	+31	0.33	1.2	122	70	92	+19	+21
112	6	54	9	12.6	18	1.42	68	2.1	7.44	1.15	+19.6	2.7	2.4	139	80	75	+ 5	+14
88	8.25	57	7	8.2	17	2.07	77	1.85	7.41	1.75	+31	0.11	2.6	140	85	68	+25	+28
91	7	56	8	67	2	7.85	2.5	- 1.7	0.30	4	136	64	76	+26	+34
63	7.5	71	9.4	11.4	20.9	1.82	62	1.5	7.63	5	+ 0.65	1.4	5	116	62	60	+ 5	+35
	6.8	58.5	8.7	10	18.6	1.86	67	1.65	7.90	2.15	- 6.5	0.60	2.67	127	72	77	+ 9.8	17

Renal Group Having Increased Blood Pressure with Urinary Changes

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
53.1	..	Arteriosclerosis	Slight granulation	7	51	208	237	19.6	9	14.4	17.6	13.4	0	20.2	5
56	+	Arteriosclerosis, dilated aorta	Normal	45	65	204	222	18	11	9.8	18.2	10	0	24.6	6.6
53.1	..	Asthenic	..	+	Normal	20	73	200	167	16.4	8.4	8.2	19.2	10.2	7.2	20.6	0
51.8	..	Sthenic	Healed	..	Normal	10	66	215	247	18.2	6.2	11	13.2	14.2	8	16	9.6
54.8	..	Arteriosclerosis	..	+	Normal	12	67	233	196	23.6	17.8	11.4	13.2	19.2	0.6	28.6	3.2
53.7						19	64.5	224	220	19	8.9	11	16.4	13.4	5	22	5

Blood Pressure and Normal Urine but with X-Ray Evidence of Arteriosclerosis or Myocarditis

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
54.5	..	Myocarditis	..	0	Normal	32	33	241	...	19.2	11.8	10.8	16.8	9.2	4.6	6.8	0
62.7	++	Arteriosclerosis	Healed	..	Normal	12	59	213	222	18.4	9.2	9.6	18.8	10.8	10.6	18.2	0
57.9	..	Arteriosclerosis	Normal	15	42	195	256	19.2	9.6	12.6	18.2	15.4	11	24.4	8.6
57	++	Myocarditis	Normal	12	53	267	280	20.4	8.6	12.4	15	10	0	22.4	0
53.3	++	Arteriosclerosis, myocarditis	Normal	5	59	270	215	22.4	9	12.2	18.2	12.2	0	18.2	0
49.5	+	Aorta, arteriosclerosis	Normal	30	60	243	222	19.6	7	9.2	14.4	11.2	0	25.6	0
55.2	+	Myocarditis	..	+	Normal	15	62	265	256	20.8	5.8	8.6	11.2	13.4	6.2	21.4	0
55.3	++	Arteriosclerosis	++	++	Normal	15	60	200	290	22	9.4	11	15	10.8	5.6	26.2	0
59	..	Arteriosclerosis	..	++	Normal	18	60	218	215	22.4	7.2	10.8	18.4	9.6	0	24	0
53.4	..	Arteriosclerosis	..	+	Normal	40	70	245	167	18	8.2	11.4	15.2	12.4	0	28.4	0
58.9	+	Arteriosclerosis	Venous capillaries tortuous	45	65	208	222	16.8	6.8	8.8	16.6	12	9.4	22	0
62.4	..	Arteriosclerosis	Healed	17	40	190	215	20	11	17.2	15.2	12.2	0	26.2	0
55.9						21	55.3	229	228	20	8.62	11.2	16.1	11.6	4	21.8	0.68

TABLE 8.—The Results of the Examinations of the Men in the Cardiovascular

Individual Number	Bilster Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate, per Cent
															Systolic	Diastolic			
14	7	74	10.5	11.2	19.6	1.75	67	1.7	8.06	1.55	— 2.7	0.20	2.1	Casts, sugar	128	80	76	0	0
55	8.5	60	7	8	24.9	3.1	73	1.5	7.75	2.75	+ 6.2	0.38	0.6	+	128	68	84	+ 5	+ 8
66	6	78	13	11	20	1.82	67	1.22	8.06	0.85	+ 1.3	0.37	3.5	+	128	66	77	+37	+44
128	15	68	3.8	9.4	19.7	2.09	70	0.8	8.06	4	—18	1	0.6	+++	122	80	84	+13	+24
49	6	60	11	11	25.2	2.29	74	4.8	8.28	5.5	+ 7.2	0.32	2	+	134	72	60	+21	+41
	8.5	67	9	10.1	21.9	2.2	72	1.14	8.16	2.93	0	0.45	1.76		128	73	76	+15	+23

TABLE 9.—The Results of the Examinations of the Men in the Cardiovascular Renal Group and Those with Roentgenographic

Individual Number	Bilster Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Wassermann Reaction	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate, per Cent
															Systolic	Diastolic			
29	6.5	72	11	10.2	26.6	2.61	69	1.9	8.28	Slight	2.25	+ 9.6	0.28	2	92	48	68	+12	+ 6
48	6.75	66	9.7	9.6	27.6	2.87	71	1.5	8.59	Slight	1.25	+ 8.5	0.10	1.6	104	72	84	+ 9	+12
73	9	60	7.6	11.2	19.5	1.74	71	2.3	8.5	Slight	2.1	+16.3	0.20	3	104	70	54	+ 3	+10
23	6	67	11.1	13.1	28.6	2.19	85	...	7.87	...	1.75	+10.9	0.42	3	102	58	82	+25	+41
82	6	52	8.6	9.21	16.7	1.81	75	2	7.51	...	1.25	+25	0.16	1.6	100	60	73	0	+ 2
105	9	62	7	9	17.1	1.81	52	1.6	7.63	...	2.5	+31.6	0.09	...	108	70	82	+26	+26
87	6	56	9.3	8.4	19.5	2.32	94	2.3	7.55	...	1.5	+18	0.42	4	102	58	60	+40	+53
97	6	54	9	8.4	20.9	2.37	60	1.4	7.85	...	1.75	+29	0.22	4.5	100	63	66	+20	+30
122	4	68	17	10.6	19.2	1.81	50	1.8	8.06	...	?	— 7	0.37	2.4	102	50	68	— 3	— 6
43	6.25	60	9.7	9.2	17.4	1.89	67	1	7.63	...	1.75	— 4.4	0.27	3.5	96	50	74	+18	+40
35	8	54	6.7	8.7	25.2	2.9	79	2	8.28	...	1.25	+12.3	0.38	2	108	78	62	+33	+47
	6.7	61	9.3	9	19.8	2.2	70.8	1.78	8		1.73	+13	0.26	2.76	101	61	71	+16	+23

Renal Group Having Normal Blood Pressure with Changes in the Urine

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
65	..	Asthenic	0	0	Normal	40	36	198	278	24.4	6.2	13.2	7.2	15	4.4	9.8	10
56.6	..	Asthenic	Healed	+	Normal	20	50	170	...	17.6	8.2	10.2	19.6	11.2	12.2	..
53.1	+	Arteriosclerosis, myocarditis	..	-?	Tortuous, beaded	30	64	257	215	20	9.2	13.6	16.6	10.2	18.2	..
58.1	..	Arteriosclerosis	Healed	..	Slight granulation	24	66	180	230	12.6	10.2	14.4	22.6	..
59.1	..	Sthenic	Normal	15	42	230	...	18.4	10.2	13	12.2	4.2	1	9	..
58.4						26	51.6	200	241	20	8.2	12.4	12.6	11	1	14.4	2

with Blood Pressure Under 110 (Including the Syphilitic Group, the Normal Group, Evidence of Healed Tuberculosis)

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
63.4	Sthenic	..	0	Normal	35	30	210	...	19.6	10	10	8.6	7.2	6.4	10.4	0
58	Sthenic	Healed	0	Tortuous	35	46	222	...	19.2	8.4	15.2	12	8	0	7	0
59.7	Asthenic	Normal	35	48	191	247	17.6	8.2	12	16	15.6	0	2	8
57.9	Sthenic	Healed	0	Normal	28	54	233	...	17.2	8.2	10.6	17.2	9.2	3.2	7.2	6
56.3	Asthenic	Healed	+	Normal	16	41	204	221	20.8	9.6	9.2	20	10.2	0	20.4	0
64.4	Asthenic	Healed	?	Normal	15	56	194	238	19.6	5.6	9.2	16	12	10.4	27.2	0
55.4	Sthenic	Normal	18	46	200	222	16	8.8	10	12.4	12	5.4	25.4	10.2
57.2	Sthenic	..	+	Dilated, U-shaped	20	53	230	245	18.2	9	9.8	16.4	12	9	32.6	0
56.8	Asthenic	Normal	5	33	189	209	20	7.8	10	6.6	12	9	21.2	0
60.1	Asthenic	Decreased	7	45	231	...	22	7.5	11.2	20.6	10	0	11	0
57.6	Sthenic	..	+	Normal	20	44	203	...	22.8	11	14.8	20.4	9.2	0	5.2	0
58.7					21	45.1	200	230	19.44	8.5	11	15.2	10.6	3.94	14.2	2

TABLE 10.—The Results of the Examinations of the Men in the Cardiovascular

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure	Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure, per Cent
36	8	58	7.2	12.1	26.3	2.17	90	2	8.28	1.25	+ 1.3	0.11	3.8	++	104	50	+12	+28
130	15	71	4.7	9.5	15.5	1.63	86	0.66	7.90	1.12	+12	0.35	...	+++	106	50
54	6	60	10	22	80	2	8.28	1.25	- 3.4	0.26	2.6	+	104	80	+65	+90
65	6	61	10	9.8	16.4	1.67	65	1.7	8.28	3	+29	0.85	0.4	++	100	70	+30	+42
76	8.5	76	9	10.8	20.2	1.87	77	2.3	8.2	1.05	+ 8	0.28	0.6	+	108	82	+11	+ 8
127	13	50	3.8	9.7	16.2	1.67	81	2	7.85	4.25	- 3.5	1.2	3	+++	108	74	+60	+54
	9.7	59	7.4	10.4	19.4	1.86	80	1.77	8.14	2.36	+ 7.2	0.51	3.9		105	71	+38	+44

TABLE 11.—Averages of the Results of the Individual

	Number in Group	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Wassermann Reaction	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure	Pulse Rate	Epinephrine, Pulse Pressure, per Cent
Table 2: Normal group.....	20	6.8	62	9.3	9.7	20.3	2.1	72.8	2.22	8.04	1.83	+ 5	0.33	3.7	...	116	70	+19.6
Table 3: Normal group with x-ray evidence of healed tuberculosis	17	7.3	64.8	9.6	10.5	20.8	1.98	71.6	2.43	7.88	2.15	+ 8	0.36	3	...	117	67	13.4
Tables 2 and 3: Average normal group	37	7	63.3	9.4	10.1	20.6	2.04	72.3	2.32	7.96	1.97	+ 6.3	0.35	3.5	...	116	69	+16.5
Table 4: Roentgenographic evidence of active tuberculosis.	9	8.4	59	7.5	9.6	20.1	2.08	70	1.4	8.08	1.9	+18.2	0.28	2.2	3/9	133	73	+11
Table 5: Increased blood pressure; urine normal.....	10	7.5	61	8.6	10.47	20.8	2	70	1.82	8.04	1.86	+11.4	0.7	4.6	0	147	83	+ 9.3
Table 6: Increased blood pressure; urine +	5	10.1	64	6.4	9.34	16.6	1.82	67	1.7	8	1.5	+ 6	0.38	4	5/5	145	76	0
Table 7: Normal blood pressure; normal urine; x-ray evidence of arteriosclerosis or myocarditis	12	6.8	58.5	8.7	10	18.6	1.86	67	1.65	7.90	2.15	+ 6.5	0.60	2.67	0	127	72	+ 9.8
Table 8: Normal blood pressure; urine +; arteriosclerosis or myocarditis.....	5	8.5	67	9	10.1	21.9	2.2	72	1.14	8.16	2.93	0	0.45	1.76	5/5	128	73	+15
Table 9: Low blood pressure; normal urine	11	6.7	61	9.3	9	19.8	2.2	70.8	1.78	8	3/11	1.73	+13	0.26	2.76	0	101	61	+16
Table 10: Low blood pressure; urine +	6	9.7	59	7.4	10.4	19.4	1.86	80	1.77	8.14	2.36	+ 7.2	0.51	3.9	6/6	105	71	+38

Renal Group Having Low Blood Pressure, with Changes in the Urine

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheel (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheel (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheel (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheel (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
57.6	Asthenic	..	0	Normal	20	43	222	...	20.8	14.2	11.2	18	7.4	0	7.4	0
55.5	Aneurysm, sthenic	Normal	15	65	196	196	20	5.4	10.8	12.6	11.2	0	22.6	0
56.6	Myocarditic cirrhosis of liver, sthenic	Normal	25	49	256	...	21.2	10.4	11	18	12	0	11.0	0
53.1	Sthenic	Tortuous	12	34	221	...	14.8	13	12	19.8	9.2	10.2	10.4	0
57.9	Arteriosclerosis, dilated aorta	Normal	10	43	230	215	20	6.6	12.4	19.6	11	7	12	0
59.1	Asthenic	Healed	..	Normal	16	65	180	247	18.4	9.4	12	10.2	15.4	12	22	0
56.6					16	49.8	218	211	19.2	9.8	11.8	16.4	11	4.8	14.2	0

Examinations Set Forth in Tables 2 to 10

Epinephrine, Pulse Pressure \times Pulse Rate, per Cent	CO ₂ Combining Power	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheel (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheel (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheel (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheel (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)	Clinical Diagnosis and X-Ray Diagnosis
+28.6	57.6	7/20	14.5	40.2	224	222	21	9.36	11.7	16.3	11.0	5.45	17.9	3.1	
20	58.5	Healed parenchymal	6/17	16.5	43.6	218	233	19.2	8.66	11	15.5	11	6.2	17	1.5	Healed parenchymal tuberculosis
+24	56	13/37	15.6	41.8	221	228	20	9	11.3	16	11.3	5.8	17.4	2.38	
+23	58.8	Active (roentgenogram)	3/9	2/7	21	58.7	215	208	20	7.2	10.6	15.6	12	6.4	18	2.6	Active parenchymal tuberculosis
+14.1	57.7	2/10	3/10	24	50.9	217	217	20.1	9.7	12	16.6	10.4	3.8	19.2	4.6	Arteriosclerosis or myocarditis (5/10 x-ray)
+4	53.7	2/5	1/5	19	64.5	224	220	19	8.9	11	16.4	13.4	5	22	5	Arteriosclerosis or dilated aorta. (3/5 x-ray)
+17	55.9	4/12	1/12	21	55.3	229	228	20	8.62	11.2	16.1	11.6	4	21.8	0.68	Arteriosclerosis or myocarditis
+23	58.4	1/5	2/5	26	51.6	200	241	20	8.2	12.4	12.6	11	1	14.4	2	Arteriosclerosis
+23	58.7	3/11	1/11	21	45.1	200	230	19.5	8.5	11	15.2	10.6	3.94	14.2	2	
+44	56.6	1/6	16	49.8	218	211	19.2	9.8	11.8	16.4	11	4.8	14.2	0		

feeling tired. The blood sugar level and the blood pressure are low, the reaction to epinephrine is vagotonic and the weight/length ratio is low.

Permeability of the Capillaries: High permeability occurs in only one man (no. 78). The history is negative other than that the man has recently had an acute attack of rheumatism.

K/Ca Ratio: A low ratio (1.43) is found in patient 17, a young laboratory technician. He has a markedly vagotonic reaction to epinephrine and shows other abnormalities. A high ratio occurs in patient 35, who is apparently normal.

Kromayer Lamp Erythema Time: Two persons (nos. 29 and 78) have prolonged Kromayer light erythema time. These men have high resistance of the skin to electric current and increased muscular irritability, as well.¹

The averages for this group of selected normal men, as compared with the averages for the entire series of 100, differ in the rapidity of the responses to cantharides, to Kromayer light and to ice, and in the lower resistance of the skin to electric current, and lower systolic blood pressure and pulse rate and the more marked reaction to epinephrine. The men are somewhat younger. Of the reactions to pharmacologic substances the wheal due to epinephrine is increased.

Healed Tuberculosis.—The group of men with roentgenologic evidence of healed parenchymal tuberculosis are slightly older. The group averages slightly higher in cholesterol, and somewhat lower in serum proteins. The Kromayer light erythema time is increased twenty minutes. The muscle irritability seems somewhat greater than for the normal group. The pulse rate is increased. The men are somewhat thinner. The intracutaneous skin reactions other than the reduction of the wheal and flare due to epinephrine show no marked deviations.

Active Tuberculosis.—When we turn to the group of men with x-ray evidence of active parenchymal lesions, several important differences make their appearance. It is probable that some of the differences are due to the increased age of the group and the associated cardiovascular renal disturbances. It should be emphasized that these men are ordinary workmen and there was no particular reason to suspect activity. The majority of the cases are undoubtedly chronic in a marked degree.

It will be noted that the blister time is longer, the permeability of the capillaries is low and, consequently, the inflammatory index is low,

1. Despite inclusion in this true "normal" group, we are inclined to consider patients 17, 29, 78 and 122 as abnormal because of their repeated deviations from apparently normal ranges for many of the tests. It was later found that patient 29 had bile in the urine.

and that the basal metabolic rate is distinctly increased, as are the muscle reactivity, the pulse rate and the ice reaction time. On closer examination (the section on the K/Ca ratio may be consulted here), it will be observed that the men can be grouped on the basis of the K/Ca ratio into those with low ratios and those with high ratios. Those with high ratios include the men with cardiovascular disturbances. Roentgenologic examination indicates that those with low ratios have asthenic hearts (all with low or normal blood pressure). Those with high ratios have sthenic hearts. Those with low K/Ca ratios have shorter reactions to the Kromayer light, lower blood pressure, lessened muscular irritability and diminished weight.

Cardiovascular Renal Groups.—If we average the cardiovascular renal group and compare it with the normal, it will be noted that the blister time is longer, the globulins considerably increased, the Kromayer light erythema time prolonged, the resistance of the skin increased, the CO_2 combining power diminished and the ice reaction prolonged. Some of these differences must, of course, be attributed to the advanced age of the men. If we contrast the men having positive urinary conditions in the cardiovascular renal group with those having no urinary changes, we find that the blister time is longer and the capillaries appear to be somewhat more permeable. There is more globulin and the resistance of the skin to electric current is lowered.

If we compare the groups having increased blood pressure (5 and 6) with the groups having normal blood pressure (7 and 8), the following differences make their appearance: The blister time in the groups with increased blood pressure is prolonged, the Kromayer lamp erythema time shortened, the basal metabolic rate heightened, the muscular irritability lessened and the vascular reaction to epinephrine diminished.

III. DETAILED STUDY OF THE "NORMAL" GROUP AND OF MISCELLANEOUS CLINICAL PATIENTS

In this part of the paper, we present the results of the clinical response to each of the various tests that we have carried out. The material consists of the 100 so-called normal men, as well as a considerable number of persons with diseases, chiefly exophthalmic goiter, glaucoma, diseases of the skin and certain vascular diseases (Raynaud's, Buerger's, etc.).

In table 1, the identification number, age, sex, occupation, nationality and clinical diagnosis of each person are presented. The identification numbers marked with an asterisk indicate persons included in the group of 100 so-called normal men.

METHOD OF PRESENTATION OF RESULTS

Since many different tests were made on each person, we proceeded to study each reaction separately, and to permit a rapid survey of the results, we adopted the following method: Results of each test for the entire group were arranged in numerical progression. A chart was made of this curve, and at the bottom of the chart we indicated the location on the curve and the clinical classification of the individuals of the group of 100 "normal" men. At the top of each chart, we usually indicated the location and clinical classification of the patients, particularly those with exophthalmic goiter and those with glaucoma. In addition to this chart, we made a tabulation of the twenty persons at each of the extreme ends of the curve and endeavored to correlate the results of other tests with the results of the one under consideration.

As the charts were all prepared in a uniform manner the first one—the chart of the blister time—is explained in some detail.

BLISTER TIME

When one analyzes chart 1, a number of features immediately present themselves. There appear to be proportionately more persons with roentgenologic evidence of healed tuberculosis in the region of the prolonged blister time with the cantharides method. The persons with roentgenologic evidence of active tuberculosis also tend to have a longer blister time. There are more of the persons showing cardiovascular renal changes in this end of the curve. This seems to apply not only to the group with urinary changes but to those with changes in the capillaries of the skin. Advancing age, increasing blister time and more frequent cardiovascular renal injury are obviously associated. The patients with glaucoma, as might be anticipated, are at the end of

TABLE 1.—General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation

Individual No.	Sex	Age	Nationality	Occupation	Clinical Notes
1	M	23	Jewish	Student	Out of school because of "nervous breakdown"
2	M	13	American	Schoolboy	Epilepsy and vasoneurosis
3*	M	25	Jewish	Instructor	Nervous; healed tuberculosis; father has Raynaud's disease
4*	M	40	American	Instructor	Normal
5	F	48	Jewish	Housewife	Nervous; cardiovascular renal condition; healed tuberculosis
6	M	49	Jewish	Painter	Arteriosclerosis and myocarditis; syphilis; died
7	M	25	American	Student	Gastric ulcer; mother died of exophthalmic goiter
8*	M	38	German	Instructor	Normal
9	M	27	American	Exophthalmic goiter
10*	M	40	Norwegian	Technician	Healed tuberculosis
11	M	46	German	Exophthalmic goiter
12	M	40	Bohemian	Painter	Traumatic atrophy of muscle
13*	M	53	American	Janitor	Healed tuberculosis
14*	M	36	German	Technician	Probably gallbladder disease; cardiovascular renal condition
15*	M	60	American	Technician	Healed tuberculosis
16	M	33	American	Exophthalmic goiter
17*	M	28	German	Student	Normal, but with marked deviations in many tests
18*	M	31	German	Carpenter	Healed tuberculosis
19	M	34	American	Clerk	Normal, but examination not completed
20*	M	42	Irish	Laborer	Roentgenographic proof of active tuberculosis
21*	M	56	German	Clerk	Cardiovascular renal condition
22	M	38	German	Machinist	Exophthalmic goiter
23*	M	54	Dutch	Machinist	Healed tuberculosis
24*	M	30	Irish	Waiter	Healed tuberculosis
25*	M	35	Austrian	Laborer	Roentgenographic evidence of active tuberculosis
26*	M	30	American	Electrician	Syphilis
27	M	30	Negro	Laborer	Syphilis; lead poisoning
28*	M	43	American	Electrician	Healed tuberculosis
29*	M	43	German	Cook	Urine contains bile pigment; subject presents a number of other abnormalities
30*	M	42	Irish	Porter	Cardiovascular renal condition
31	F	42	American	Housewife	Exophthalmic goiter
32*	M	26	American	Salesman	Cardiovascular renal condition
33	M	37	American	Laborer	Epileptic
34*	M	41	American	Railroad worker	Changes in capillaries of the skin; healed tuberculosis
35*	M	44	German	Clerk	Normal
36*	M	43	American	Clerk	Cardiovascular renal condition
37*	M	45	Irish	Miner	Normal
38	M	39	Jewish	Druggist	Angioneurotic edema
39*	M	35	Polish	Porter	Syphilis
40*	M	40	German	Houseman	Capillaries of the skin abnormal
41*	M	40	English	Machinist	Normal
42*	M	33	American	Fireman	Cardiovascular renal condition (myocarditis)
43*	M	45	American	Steamfitter	Normal
44*	M	48	American	Porter	Normal
45*	M	39	American	Painter	Cardiovascular renal condition
46*	M	29	American	Carpenter	Inanition; died later at Cook County Hospital (bronchopneumonia); fainted during examination
47*	M	38	American	Painter	Healed tuberculosis
48*	M	46	American	Woodworker	Syphilis
49*	M	42	Italian	Laborer	Cardiovascular renal condition
50*	M	20	German	Mason	Normal
51	F	56	German	Housewife	Exophthalmic goiter
52*	M	36	German	Steel worker	Healed tuberculosis
53*	M	30	Swedish	Laborer	Normal
54*	M	49	American	Fireman	Cardiovascular renal condition; probably cirrhosis; myocarditis
55*	M	51	American	Metal worker	Cardiovascular renal condition
56*	M	44	English	Fireman	Roentgenographic evidence of active tuberculosis 3 years before; angioneurotic edema
57	F	30	German	Housewife	Postoperative hypothyroidism; on thyroid extract, with basal metabolic rate +31.5

* One of group of 100 "normal" men.

TABLE 1.—General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation—Continued

Indi- vidual No.	Sex	Age	Nationality	Occupation	Clinical Notes
58	F	29	American	Housewife	Exophthalmic goiter
59*	M	37	Irish	Butcher	Normal
60	M	52	American	Salesman	Cardiovascular renal condition
61*	M	51	American	Musician	Cardiovascular renal condition
62*	M	44	American	Carpenter	Cardiovascular renal condition; aortic regurgitation
63*	M	40	American	Fireman	Cardiovascular renal condition
64*	M	31	American	Machinist	Normal, somewhat nervous
65*	M	34	American	Fireman	Cardiovascular renal condition
66*	M	64	American	Engineer	Cardiovascular renal condition
67*	M	47	American	Porter	Dwarf
68*	M	35	American	Draftsman	Healed tuberculosis
69	M	22	Jewish	Student	Duodenal ulcer; nervous; parents both have high blood pressure
70*	M	65	German	Butcher	Cardiovascular renal condition; arthritis deformans
71*	M	42	Scotch	Cook	Cardiovascular renal condition
72*	M	42	Scotch	Laborer	Normal
73*	M	48	American	Engineer	Syphilis
74*	M	49	American	Clerk	Changes in the capillaries of the skin
75*	M	66	American	Laborer	Cardiovascular renal condition
76*	M	43	American	Cook	Cardiovascular renal condition
77*	M	39	Irish	Machinist	Sensitized; drug addict?
78*	M	33	American	Painter	Normal, but with many deviations in examinations
79*	M	58	American	Machinist	Gastric ulcer; occasional peripheral vascular spasms
80*	M	29	American	Electrician	Nervous; has tremor; urticaria in 1922
81*	M	69	American	Elevator operator	Cardiovascular renal condition; pruritis
82*	M	66	English	Laborer	Cardiovascular renal condition
83*	M	45	German	Fireman	Normal
84*	M	73	Canadian	Foundry worker	Cardiovascular renal condition
85*	M	45	American	Tile setter	Fever (bronchitis?)
86*	M	50	American	Exdentist	Nervous
87*	M	46	American	Chauffeur	Normal
88*	M	55	American	Factory worker	Roentgenographic evidence of active tuberculosis
89*	M	41	Irish	Sailor	Healed tuberculosis
90*	M	30	American	Mail sorter	Nervous
91*	M	91	Irish	Gardener	Cardiovascular renal condition
92*	M	22	Jewish	Student	Nervous
93*	M	53	American	Laborer	Cardiovascular renal condition; hay-fever
94*	M	57	American	Laborer	Normal
95*	M	54	German	Cook	Healed tuberculosis
96*	M	70	American	Ironworker	Cardiovascular renal condition
97*	M	53	American	Miner	Normal; nervous
98*	M	34	American	Railroad worker	Cardiovascular renal condition
99*	M	46	Norwegian	Laborer	Healed tuberculosis
100*	M	45	Norwegian	Laborer	Healed tuberculosis
101*	M	55	American	Laborer	Eczema
102*	M	65	American	Metal worker	Roentgenographic evidence of active tuberculosis
103*	M	59	American	Rancher	Cardiovascular renal condition
104*	M	76	American	Laborer	Roentgenographic evidence of active tuberculosis; cardiovascular renal condition
105*	M	56	American	Painter	Healed tuberculosis
106*	M	60	American	Cook	Cardiovascular renal condition
107*	M	62	American	Sailor	Cardiovascular renal condition
108*	M	67	American	Clerk	Roentgenographic evidence of active tuberculosis
109	F	42	American	None	Neurasthenia
110*	M	62	American	Teamster	Healed tuberculosis
111*	M	60	American	Clerk	Cardiovascular renal condition; syphilis 30 years before
112*	M	60	American	Wool sorter	Cardiovascular renal condition
113*	M	59	Irish	Butcher	Cardiovascular renal condition
114*	M	79	English	Engineer	Roentgenographic evidence of active tuberculosis; cardiovascular renal condition
115*	M	66	American	Telegrapher	Cardiovascular renal condition
116	F	30	English	Clerk	Urticaria
117	M	30	English	Stockman	Arthritis; syphilis
118	F	14	American	Schoolgirl	Arthritis; pleural tuberculosis?

* One of group of 100 "normal" men.

TABLE 1.—General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation—Continued

Individual No.	Sex	Age	Nationality	Occupation	Clinical Notes
119	F	43	Dutch	Housewife	Arthritis deformans; adenoma of thyroid with hyperthyroidism
120	F	18	Hungarian	Housework	Purpura
121	F	56	American	Housewife	Arthritis deformans
122*	M	33	American	Instructor	Normal; fatigue; numerous deviations from normal in examinations
123	F	68	American	Housewife	Carcinoma of thyroid; hyperthyroidism; cardiovascular renal condition
124	F	25	American	Nurse	Arthritis with mitral lesion
125	F	29	American	Housewife	Exophthalmic goiter
126	M	21	American	Metal polisher	Exophthalmic goiter
127*	M	65	Irish	Janitor	Cardiovascular renal condition
128*	M	66	American	Railroad worker	Hay-fever; cardiovascular renal condition
129*	M	66	Irish	Janitor	Roentgenographic evidence of active tuberculosis; cardiovascular renal condition
130*	M	65	Irish	Mason	Cardiovascular renal condition
131	F	59	Austrian	Housewife	Exophthalmic goiter
132	M	26	American	Student	Eczema
133	F	29	Jewish	Housewife	Generalized scleroderma
134*	M	67	American	Carpenter	Cardiovascular renal condition
135	M	26	Jewish	Tailor	Nervous
136	M	44	Italian	Laborer	Pellagra; cardiovascular renal condition
137	F	61	Bohemian	Housewife	Glaucoma
138	M	27	Jewish	Salesman	Fröhlich's syndrome
139	F	29	American	Stenographer	Vitiligo and urticaria
140	M	45	Irish	Laborer	Glaucoma; cardiovascular renal condition; roentgenographic evidence of active tuberculosis; hay-fever
141	F	48	Negro	Housewife	Glaucoma; cardiovascular renal condition
142	M	50	American	Machinist	Brain tumor, Cook County Hospital; syphilis 20 years before
143	M	45	Hungarian	Carpenter	Pellagra; cardiovascular renal condition; syphilis
144	M	47	Lithuanian	Carpenter	Pellagra; cardiovascular renal condition
145	M	71	Swedish	Watchman	Glaucoma; syphilis
146	F	40	American	Sewing	Myasthenia gravis
147	F	19	Polish	Operator	Postencephalitic parkinsonism
148	F	67	American	Housewife	Glaucoma; vitiligo; hay-fever
149	M	35	American	Salesman	Nervous
150	M	67	Jewish	Teamster	Glaucoma
151	F	68	German	Housewife	Postoperative exophthalmic goiter (no. 51)
152	M	27	American	Plumber	Angioneurotic edema
153	M	75	American	Farmer	Glaucoma; cardiovascular renal condition
154	M	55	American	Steel worker	Glaucoma; cardiovascular renal condition
155	M	33	American	Engineer	Postoperative exophthalmic goiter (no. 16)
156	F	30	American	Housewife	Postoperative exophthalmic goiter (no. 125)
157	M	38	American	Plumber	Postoperative exophthalmic goiter (no. 22)
158	M	35	Bohemian	Butcher	Hodgkin's disease
159	M	53	American	Clerk	Exophthalmic goiter
160	M	58	English	Shoemaker	Glaucoma; cardiovascular renal condition; asthma
161	F	43	American	Housewife	Glaucoma; cardiovascular renal condition
162	M	47	German	Railroad worker	Postoperative exophthalmic goiter (no. 11)
163	F	29	American	Housewife	Postoperative exophthalmic goiter (no. 58)
164	M	48	Cuban	Salesman	Glaucoma; syphilis; cardiovascular renal condition
165	M	52	American	Upholsterer	Glaucoma; cardiovascular renal condition
166	M	24	Hindoo	Student	Asthenia; eosinophilia
167	F	77	Swiss	Housewife	Glaucoma; cardiovascular renal condition
168	M	28	American	Physician	Orthostatic albuminuria
169	M	27	American	Chauffeur	Buerger's disease; syphilis
170	F	56	Negro	Servant	Glaucoma; diabetes; cardiovascular renal condition
171	F	23	Jewish	Technician	Urticaria (menstrual)
172	M*	30	Greek	Waiter	Raynaud's disease; syphilis in 1921
173	M	39	American	Instructor	Cord tumor
174	F	50	American	Housework	Raynaud's disease

* One of group of 100 "normal" men.

Chart 1.—The scale of the blister time (heavy line) of normal persons and patients with various clinical conditions.

It will be observed that the blister time varies from a short time of $3\frac{1}{2}$ hours in one case to 15 hours in a group of cases. The average for our group of 100 "normal" men is $7\frac{1}{2}$ hours; this is indicated by the horizontal line.

Persons of the actually normal group (twenty in number) are designated by a star in the circle, in the first line below the curve. The range for these is from 4 to 9 hours. As the person (no. 122) with the four-hour blister time is abnormal in several other respects, we have not considered 4 hours as within the true normal range. The normal range is indicated by the shaded diamond in the center of the chart, in case of normal blister time having been placed between 6 and 9 hours.

Individuals of the group who showed healed tuberculosis are indicated by the large crosses in the next line. Individuals of the group with cardiovascular renal conditions of the group who gave roentgenologic evidence of healed tuberculosis are indicated by a small cross placed in the same horizontal space. The persons with positive Wassermann reactions and those with a clear history of previous syphilis are indicated by *W* in the same space. Patients who gave roentgenologic evidence of active tuberculosis can be identified by a black block in the third horizontal space. Those in the various groups of the division with cardiovascular renal conditions can be identified by the devices in the five lowest horizontal compartments, as follows:

- A patient having a low blood pressure (under 110) with the urine containing either albumin or casts.
- ⊗ A patient having a normal blood pressure (from 110 to 140) with positive evidence of urinary changes.
- A patient having a blood pressure of over 140 with positive evidence of urinary changes.
- ⦿ A patient having a blood pressure of over 140 with no evidence of changes in the urine.
- ⊙ A patient having roentgenologic evidence of arteriosclerosis of the larger vessels. When this has been found incidental to other clinical conditions, a small circle has been used.
- A person in whom the capillaries of the skin are abnormal. A small *c* has been used to indicate that changes in the capillaries of the skin have been found incidental to other clinical conditions.

All the large symbols used in these lower five horizontal columns refer to the group of 100 "normal" men.

At the top of the curve we have used *G* to indicate the patients with glaucoma and \times *G* to indicate those with exophthalmic goiter. In some charts, the individual numbers of the patients have been appended in the uppermost horizontal column.

An *N* along the curve indicates a nervous person, and an *S* a person who has been sensitized.

This explanation applies to all charts.

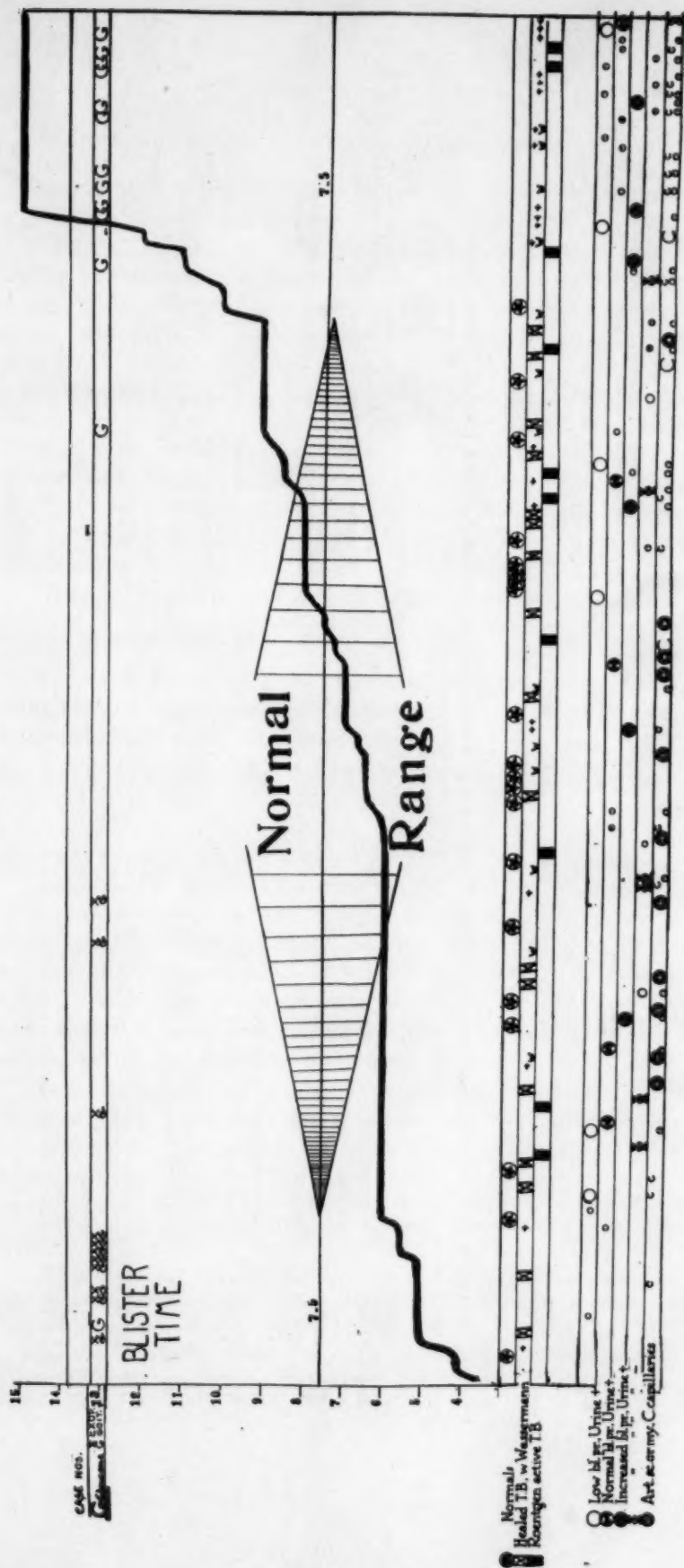


Chart 1

TABLE 2.—The Results of Examinations of the Twelve Persons with the Shortest Blister Time

Individual Number	Blister Time, Hours	Diagnosis	Calcium, Mg.	Potas- sium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Minutes	Age	Ice Reaction Time, Seconds	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Changes in Capillaries Urine)	Arterio-sclerosis and Changes in Urine
116	3.5	Urticaria	10	19.4	1.94	30	30	30	Vagotonic	20.4	7.4	..
169	4	Urticaria and nervous Angioneurotic edema	9.6	18.1	1.85	120*	22	20	Sympathetotonic	21.2	10	..
152	4	Normal	9.8	20.1	2.05	60	27	15	Vagotonic	26	7.5	..
122*	4.25	Urticaria	10.6	19.2	1.81	...	23	5	Vagotonic	30	7.8	..
47*	5	Healed tuberculosis	10.4	26.2	2.51	...	23	15	Vagotonic
124	5	Heart disease; arthritis	10.5	26.2	2.51	90	38	10	Vagotonic	21.6	6.2	..
161	5	Glaucoma	9.17	18.03	1.93	75	23	12	Sympathetotonic	15.2	2.6	Tracet
171	5	Urticaria	12.66	17.89	1.42	75	23	30	Sympathetotonic	17	13	Tracet
38	5	Angioneurotic edema	9.8	21	2.14	90	30	10	Vagotonic	17	16.5	..
10*	5.5	Healed tuberculosis	10.1	24.6	2.4	150	40	7	Vagotonic	18	8.6	..
5	5.5	Neurosis	11.9	25.7	2.16	75	48	..	Vagotonic	22.4	8.4	Tracet
Averages	4.6		10.4	20.81	2.005	85.5	32.7	13.4		19.58	8.1	

* One of group of 100 "normal" men.
† Albumin.

TABLE 3.—The Results of Examinations of the Twenty-Three Persons with a Prolonged Blister Time of Fifteen Hours

Individual Number	Blister Time, Hours	Diagnosis	Calcium, Mg.	Potas- sium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Minutes	Age	Ice Reaction Time, Seconds	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Changes in Capillaries Urine)	Arterio-sclerosis and Changes in Urine
167	15	Glaucoma	12	22.7	1.89	120	77	5	Sympathetotonic	17	14	..
156	15	Glaucoma	12	21.3	1.78	65	67	7	Vagotonic	17	14	..
88*	15	Nervous	12.6	15.9	1.26	105	50	25	Sympathetotonic	18.8	14	..
145	15	Glaucoma	10.1	15.7	1.55	180	71	20	Sympathetotonic	18	13.6	Arteriosclerosis + and Wasser- mann + + + +
146	15	Myasthenia gravis	9.2	14.4	1.56	105	40	30	Vagotonic	18	12	..
148	15	Glaucoma	8.7	24.3	2.8	85	67	10	Vagotonic	18	12	..
147	15	Parkinsonism	9.8	17.7	1.79	105	19	25	Sympathetotonic	18	11.6	..
144	15	Pellagra	9.7	16.6	1.74	120	47	10	Sympathetotonic	14.4	11.5	..
140	15	Pellagra	9.7	16.6	1.74	110	45	15	Sympathetotonic	16.6	11.3	..
158	15	Hodgkin's disease	9.33	15.3	1.64	60	49	35	Sympathetotonic	19.2	11.3	Albumin
169	15	Buerger's disease	12.34	18.24	1.56	125	27	25	Vagotonic	20.8	11	Albumin
107*	15	Glaucoma	8.1	18.2	2.24	130	61	30	Vagotonic	15.4	10.5	positive
154	15	Glaucoma	9	23.68	2.63	90	55	30	Sympathetotonic	23.6	10	..
104*	15	Cardiovascular renal condition	9.9	15.4	1.56	80	67	12	Sympathetotonic	23.6	9.8	..
106*	15	Pellagra	10	18.8	1.88	105	44	45	Sympathetotonic	20	9.5	..
79*	15	Urticaria	11.2	20	1.78	240	58	20	Sympathetotonic	19.2	9.4	..
100	15	Glaucoma and tuberculosis	10.86	21.58	1.98	70	58	10	Vagotonic	16	8	..
140	15	Glaucoma	11.4	20.7	2.61	150	45	45	Vagotonic	18	8	..
170	15	Glaucoma	10.6	23.7	2.2	150	56	56	Vagotonic	18	7	..
129*	15	Tuberculosis	11.5	19	1.65	90	63	17	Vagotonic	18.4	7	..
155	15	Glaucoma	9	18.7	2.08	90	75	30	Sympathetotonic	22	6.5	..
130	15	Cardiovascular renal condition	10.4	15.5	1.49	120	65	15	Sympathetotonic	20	5.4	..
128*	15	Cardiovascular renal condition	10.2	19.7	1.93	240	66	24	Sympathetotonic
Averages	15		10.4	19.5	1.86	118	55.4	21.3		18.6	10.4	..

* One of group of 100 "normal" men.

the curve representing increased blister time; those with exophthalmic goiter are at the end representing shortened blister time.

In tables 2 and 3, we present the details of the examinations of the twelve persons with the shortest blister times and of the twenty-three with a blister time of approximately fifteen hours. In practically all other tabulations, we have selected the twenty showing the extreme reactions.¹

From tables 2 and 3, the following conclusions seem warranted: Of the twenty-three persons with a prolonged blister time (table 2), twenty show roentgenologic evidence of arteriosclerosis, a positive Wassermann reaction or urinary changes (90 per cent). In the group with the shortest blister times there are none with arteriosclerosis, only one with capillary change and four (25 per cent) with trace of albumin in the urine.

The group in which blister formation is prolonged has a slightly lower level of potassium and a lower K/Ca ratio. The Kromayer light erythema time is longer, as is the reaction to ice. The persons are much older. There are fewer vagotonic reactions to epinephrine and, though the wheal due to the intracutaneous injection of epinephrine hydrochloride is small, the flare is large.

It will be noted that the types of diseases of the one group are different from those of the other group.

CAPILLARY PERMEABILITY

Permeability of the capillaries of the skin, as estimated by the relative proportion of protein in a cantharides blister as compared with the protein in the serum of the capillary blood, averages 62 for the group of 100 "normal" men. In a previous study² of sixty-six normal students in an age group of from 22 to 25, we found the average permeability to be 68, and in another study³ of a small group of young women during the intermenstrual period, we found it to be 72.

The average for our strictly normal group is also 62. When we examine chart 2, we find that a number of the normal persons are grouped at the low end of the scale. In three of the four lowest,

1. Patients with exophthalmic goiter have not been included because we have felt that the extreme changes associated with the disease might tend to distort the averages.

2. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Skin Blister, *Arch. Int. Med.* **38**:663 (Nov.) 1926.

3. Petersen, W. F., and Milles, G.: The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, *Arch. Int. Med.* **38**:730 (Dec.) 1926.

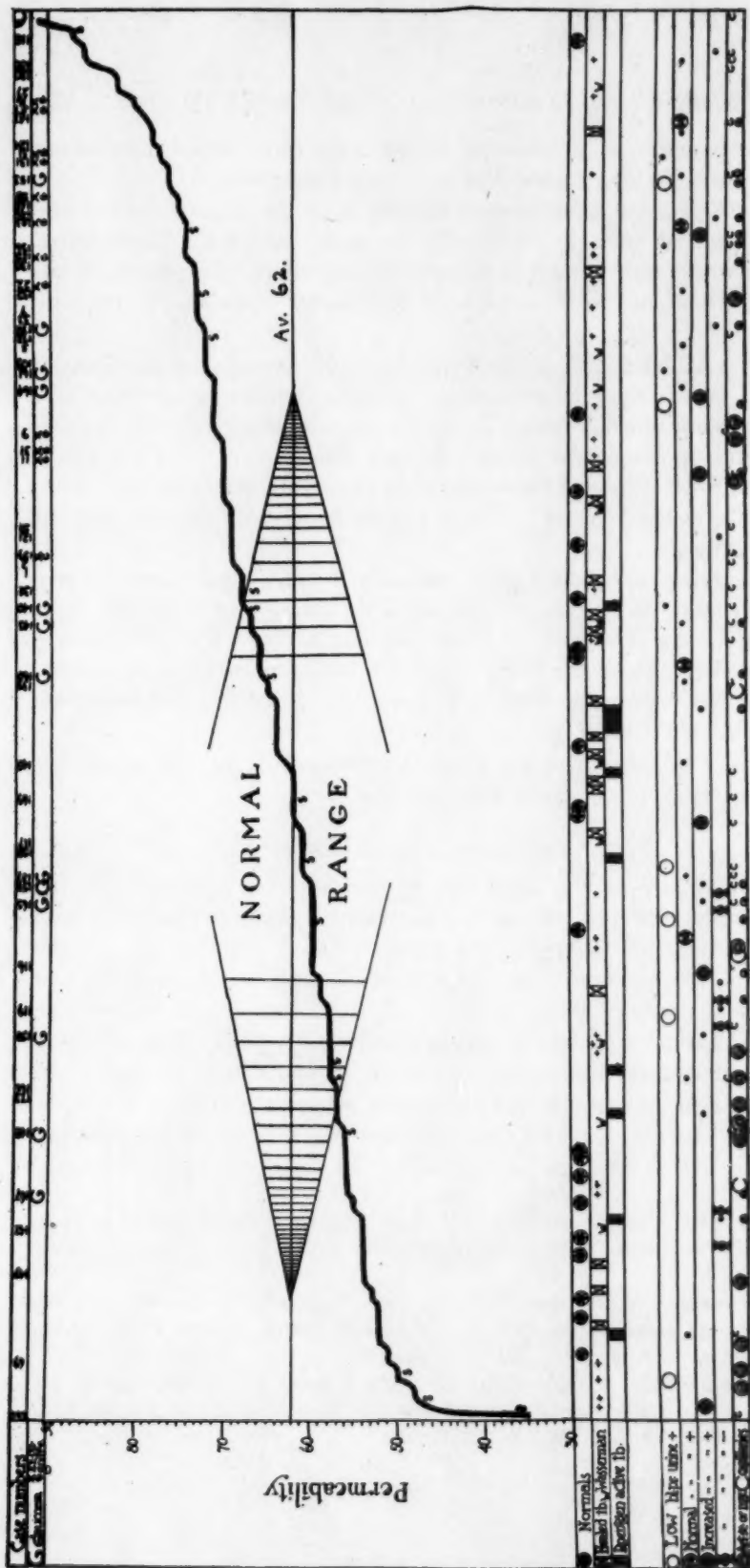


Chart 2.—The permeability of the capillaries of the skin (indicated by heavy line) of normal persons and patients with various clinical conditions. An explanation of the grouping of the normal persons and patients along the curve is given in the legend for chart 1.

TABLE 4.—*The Results of Examinations of the Twenty Persons Having the Lowest Permeability of the Capillaries*

Individual Number	Permeability of Capillaries	Diagnosis	Epinephrine, Wheel (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Thyroxin, Wheel (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Weight/Length Ratio	Age	Changes in Capillaries	Changes in Urine
144	35	Pellagra	14.4	11.5	15	0	174	47	+++	0
115	46	Cardiovascular renal condition	17.2	6.2	14.2	8	215	66	..	Trace albumin
101	47	Sensitized	19.6	7	10	0	191	55	Dilatation	..
42	47	Cardiovascular renal condition	19.2	11.8	9.2	4.6	241	33
127	50	Cardiovascular renal condition	18.4	9.7	15.4	12	180	65	..	Albumin, casts
93	50	Cardiovascular renal condition; sensitized	20.4	8.6	10	0	267	52	0	..
69	51	Nervous and ulcer	21.2	10	14.4	10.2	160	22
53	51	Normal	17.2	9.2	13.4	11	258	45	Delayed	..
103	52	Cardiovascular renal condition	22.4	9	12.2	0	270	59
129	52	Tuberculosis; cardiovascular renal condition	18.4	7	12.7	0	249	66	Granulation, sluggish	Casts
80	52	Healed tuberculosis	20.8	9.8	10.2	0	204	41
59	52	Normal	22	7.2	15.6	8	252	37
62	52	Aortic regurgitation	17.2	7	11.4	7.8	221	44
94	53	Normal	20	6	11.2	7.8	236	57	Slow	..
100	53	Healed tuberculosis	18.8	8.6	12	29.2	241	45
112	54	Cardiovascular renal condition	22.4	7.2	9.8	0	218	60
149	54	Nervous	20	9.7	19	0	309	35
110	54	Edema; healed tuberculosis	20.8	4.2	12	9.4	190	62	Diminished	..
35	54	Normal	22.8	11	9.2	0	203	44
45	54	Cardiovascular renal condition	20.4	9.8	16.4	12	317	39
50		Averages and totals	19.6	8.5	12.7	6	224	48.7	2 (granulation)	3

TABLE 5.—*The Results of Examinations of the Twenty Persons Having the Highest Permeability of the Capillaries*

Individual Number	Permeability of Capillaries	Diagnosis	Epinephrine, Wheel (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Thyroxin, Wheel (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Weight/Length Ratio	Age	Changes in Capillaries	Changes in Urine
80	91	Nervous	14.8	12.4	13.4	9.2	211	29	Granulation	..
77	87	Sensitized	14	10.8	10	15.4	187	39
118	87	Arthritis, tuberculosis	16.8	7.4	12	8.6	154	14
78	86	Normal	19.6	12	12.4	6.2	203	33
79	86	Ulcer	19.2	9.4	8.2	12.2	220	58	Tortuosity	..
135	84	Nervous	12.4	3.2	20	0	183	26	Granulation	Casts
120	82	Purpura	21.2	7.2	12.1	0	172	18	Granulation	..
92	82	Nervous	20.4	10.2	15.2	7.6	210	22
27	82	Lead poisoning and syphilis	217	30
147	79	Parkinsonism	18	11.6	13	0	142	19
66	78	Cardiovascular renal condition	20	9.2	10.2	6	257	64	Granulation	+
68	78	Healed tuberculosis	19.2	9.6	12	7	217	35	Rapid flow	Trace albumin
124	78	Arthritis; heart disease	15.2	2.6	210	25	Diminished flow	..
153	76	Glaucoma, decompensation	22	6.5	18	0	223	75	Dilatation	+ Casts
76	76	Cardiovascular renal condition	20	6.6	11	7	230	43	..	Granular casts
168	75	Orthostatic	18	16	14	0	215	28	..	Albumin
146	75	Myasthenia	18	12	19	0	192	40
14	74	Cardiovascular renal condition	24.4	6.2	15	5	198	36	..	Casts
70	74	Cardiovascular renal condition	18	11	10	0	204	65	Slow	Casts, albumin
136	74	Pellagra	20	9.5	18	0	180	44	Granulation	Albumin
80		Averages and totals	18.3	9.1	13.4	4.3	204	37	7 (granulation)	9

the examination of the capillaries of the skin revealed that the capillary flow was sluggish or that the number of capillaries was diminished. While, therefore, we cannot regard these persons as abnormal, the change in the flow of the capillaries of the skin must be considered in connection with their diminished permeability. On the other hand, we note that the end of the scale representing higher permeability reveals more persons in whom distinct anatomic changes could be observed in the capillaries in the form of granulations, marked dilatations, etc.

Healed tuberculosis (revealed by roentgen examination) is found at all levels, but the cases in which there is roentgenologic evidence of active tuberculosis are found at the normal or lower levels of permeability. It should be emphasized that these cases are not necessarily clinically active; in the clinically active cases, the tendency is toward greater permeability with progression of the disease.⁴ (In chart 2, persons with roentgenologic evidence of healed tuberculosis other than those of the group of 100 "normal" men are indicated by the cross in the horizontal column designated "Healed Tuberculosis.")

It will be noted that the arteriosclerotic or myocarditic (revealed by roentgen examination) cases are equally common in both regions of the scale. But of the eighteen persons with arteriosclerosis on the side of lower permeability, only five have urinary changes, while of the seventeen on the side of higher permeability, ten have urinary changes.

There are, furthermore, nine with increased blood pressure (over 140), but without urinary changes, in the group of less permeability as compared with four in the group of more permeability.

Capillary changes, i. e., granulations, occur in eleven in the group below the average and in twenty in the group above.

Sensitized persons are reported in all the ranges.

The increased permeability coincident with exophthalmic goiter is apparent.

In table 4, we have tabulated the results of some examinations of the twenty persons with the lowest permeability and in table 5, of those with the highest permeability (excluding those with exophthalmic goiter).

When we examine the averages of tables 4 and 5, we find, of course, that the persons with lessened permeability are older and heavier.

INFLAMMATORY INDEX

The group with low inflammatory indexes is partly identical with a series showing prolonged blister time, i. e., persons of advanced age, with cardiovascular renal lesions or with other evidences of chronic disease.

4. Levinson, S. A., and Petersen, W. F.: *Am. Rev. Tuberc.* **15**:681, 1927; part vii, this series.

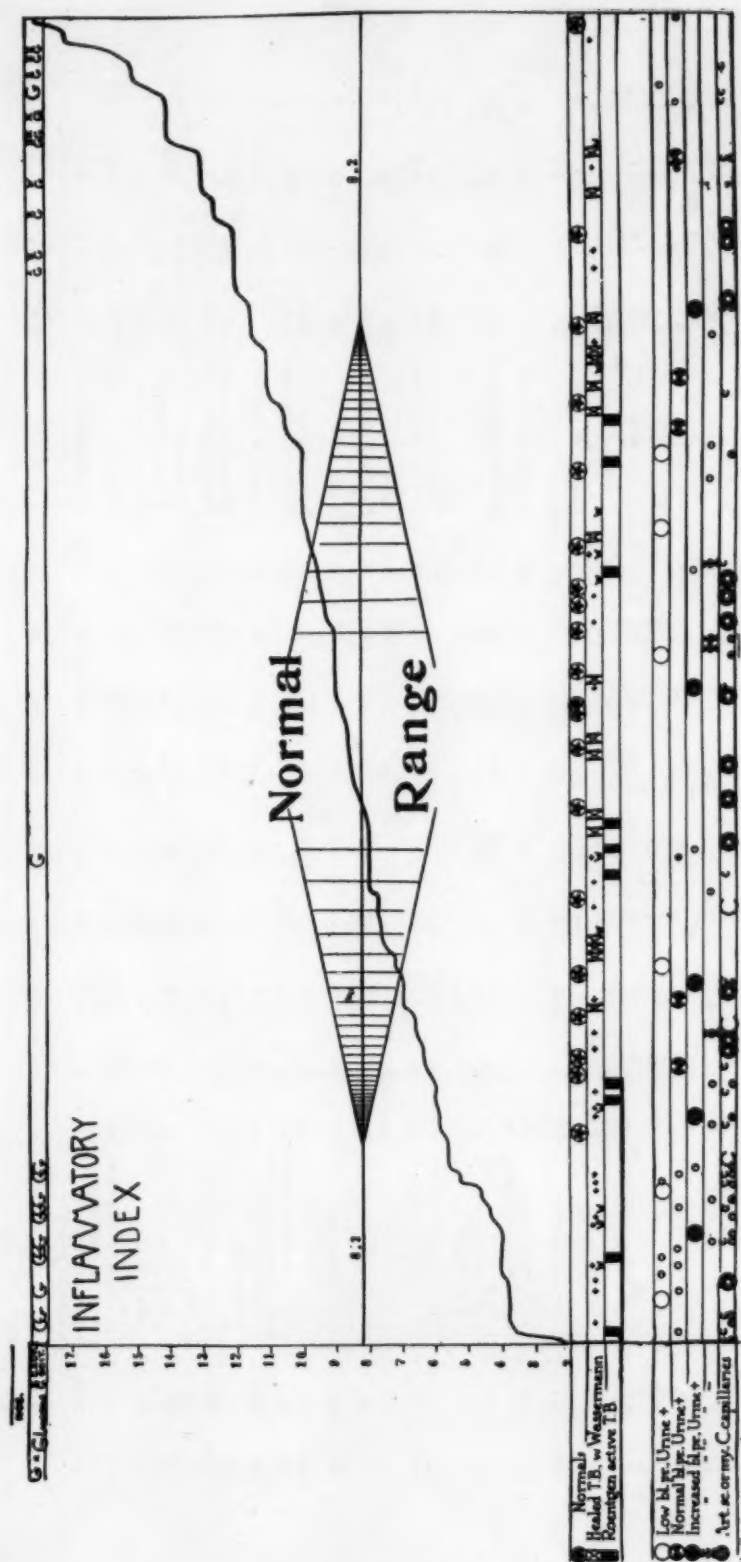


TABLE 6.—The Results of the Examinations of the Twenty Persons Having the Lowest Inflammatory Indexes

Individual Number	Inflammatory Index	Diagnosis	Bilster Time, Hours	Permeability of Capillaries	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Min.	Carbon Dioxide Combining Power	Ice Reaction Time, Seconds	Age	Kephphrine, Vascular Reaction	Kephphrine, Wheal (Diameter, Mm.)	Kephphrine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)
136	5	Pellagra	15	74	10	18.8	1.88	105	57.9	45	44	Sympathetonic	20	9.5	18	0
137*	4.7	Cardiovascular renal condition	15	71	10.4	15.5	1.49	120	55.6	15	65	20	5.4	11.2	0
170	4.6	Aortic syphilis; bronchiectasis; glaucoma	15	72	10.5	23.7	2.2	...	52.5	..	56
145	4.4	Glaucoma	15	67	10.1	15.7	1.55	180	55.4	20	71	Sympathetonic	18	13.6	16	0
100	4.4	Asthma; emphysema; bronchiectasis; glaucoma	15	66	10.8	21.5	1.98	70	62.7	10	58	Sympathetonic	16	8	20	0
169	4.1	Buerger's disease	15	62	12.3	10.2	1.56	130	55.1	25	27	Vagotonic	20.8	11	18	0
134*	4	Cardiovascular renal condition	15	60	9.9	15.4	1.56	80	54.8	12	67	Sympathetonic	23.6	9.8	19.2	9.6
154	4	Glaucoma	15	60	...	23	...	90	56.6	20	66.6	Vagotonic	23	10	26	0
137	4	Cardiovascular renal condition; glaucoma	15	61	8.1	18.2	2.24	130	51.9	30	61	Sympathetonic	15.4	10.5	13	0
140	4.05	Cardiovascular renal condition; glaucoma	15	68	11.4	28.7	2.61	150	55.6	40	45	Vagotonic	18	8	27	0
143	4	Pellagra	15	63	9.7	16.9	1.74	100	55.4	15	45	Sympathetonic	16.6	11.3	9	0
138	4	Hodgkin's disease; cardiovascular renal condition	15	61	9.3	18.5	2	60	57.8	35	49	Sympathetonic	19.2	11.3	28	0
128*	3.8	Cardiovascular renal condition	15	58	10.2	10.7	1.93	240	58.1	24	66	Sympathetonic	14.4	0
150	3.8	Glaucoma	15	58	12	21.3	1.78	95	72.7	7	67	Sympathetonic	17	14	16	0
127*	3.8	Cardiovascular renal condition	13	50	12.2	16.2	1.67	255	59.1	16	65	Sympathetonic	18.4	9.7	15.4	12
89*	3.9	Nervous	15	58	12.6	15.9	1.26	105	55	25	59	Vagotonic	18.8	14	15.4	12.4
148	3.7	Glaucoma	12	56	9.7	24.3	2.5	85	49.5	10	67	Sympathetonic	18	12	17	0
167	3.7	Bronchiectasis; glaucoma	15	56	12	22.7	1.9	120	47.9	5	77	17	14.2	15	0
129*	3.5	Tuberculosis; cardiovascular renal condition	15	52	11.5	10	1.05	90	61.6	17	66	Vagotonic	18.4	7	12.2	0
144	2.2	Cardiovascular renal condition; pellagra	15	35	9.8	17.6	1.76	130	54.4	10	47	Sympathetonic	14.4	11.5	15	0
3.97	Averages and totals		14.9	60	10.6	19.64	1.85	121.8	57.48	20	57.4	5 V., 11 S.	18.47	10.6	17.14	11.3

* One of group of "normal" men.

TABLE 7.—The Results of Examinations of the Twenty Persons Having the Highest Inflammatory Indexes

Individual Number	Inflammatory Index	Diagnosis	Bilateral Time, Hours	Permeability of Capillaries	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Min.	Carbon Dioxide Combining Power	Ice Reaction Time, Seconds	Age	Reaction	Epinephrine, Wheel (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Thyroxin, Wheel (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)
142	18	Angioneurotic edema	4	73	9.8	20.5	2.05	60	63.4	15	27	Vagotonic	26	7.5	9	8
125*	17	Normal	4	68	10.6	19.2	1.81	..	56.5	5	33	Sympathetictonic	20	7.8	12	9
116	17	Urticaria	3.5	60	10	19.4	1.94	100	55.1	20	30	Vagotonic	20.4	7.4	5	0
90*	15.1	Cardiovascular renal condition; nervous	6	91	8.1	13.7	1.7	100	53.2	30	29	Sympathetictonic	14.8	12.4	13.4	9.2
124	15	Heart disease	5	78	90	53.7	10	25	Vagotonic	15.3	2.6
161	14.5	Cardiovascular renal condition; glaucoma	5	72	9.17	15.03	1.56	75	49.4	12	43	Sympathetictonic	14	13	13	0
88	14	Cardiovascular renal condition; angioneurotic edema	5	69	9.8	21	2.14	90	58.5	10	39	Vagotonic	18	8.6	10.2	10.4
135	14	Neurovascular syndrome	6	84	11.9	19.6	1.65	75	54.5	18	28	Vagotonic	12.4	8.2	20	0
171	14	Urticaria	5	73	12.66	17.89	1.42	75	43.7	20	18	17.5	10.5	18	0
27	13.6	Lead poisoning	6	83	11.8	21.4	2.14	150	51.9	..	39
10*	13	Neurovascular syndrome; healed tuberculosis	5	64	10.1	24.6	2.4	150	60.4	7	40	Sympathetictonic	22.4	8.4	9	7.2
66*	13	Cardiovascular renal condition	6	78	11	20	1.82	15	53.1	28	54	Sympathetictonic	20	9.2	10.2	0
5	13	Nervous	5.5	72	11.9	25.7	2.16	75	63.9	..	48
120	13	Purpura	6	57	10	19.9	1.99	75	52.2	14	18	7.2	12.1
47*	12.6	Healed tuberculosis	5	62	10.4	23.2	2.31	90	56.4	15	38	Vagotonic	21.2	5.2	9	0
69	12.7	Ulcer; nervous	4	51	9.6	16	1.63	120	54.8	20	22	Sympathetictonic	21.2	10	14.4	10.2
79*	12.6	6	76	120	57.5
96*	12.1	Cardiovascular renal condition	6	73	8.3	17	1.63	105	62.7	15	34	Sympathetictonic	20	4	11.2	0
78*	12	Normal	7	86	8.4	18.8	2.23	195	62.7	10	33	Sympathetictonic	19.6	12	12.4	6.2
106*	12	Cardiovascular renal condition	6	71	11.2	19	1.69	90	49.5	30	60	Vagotonic	19.6	7	11.2	0
13.92	Averages and totals		5.3	73.2	10.17	19.9	1.95	90.5	56.07	16.4	34	8 V., 8 S.	19	8	11.8	8.6

* One of group of 100 "normal" men.

If we examine chart 3, we observe the piling up of persons with arteriosclerosis, capillary changes and evidence of renal disease (albumin or casts) at the low end of the scale. It may also be observed that the majority of the patients with roentgenologic evidence of active tuberculosis are found in the low range, where, too, there are more persons with roentgenologic evidence of healed lesions. The patients with glaucoma and the associated prolonged blister time are also in this region.

The persons with high inflammatory indexes include those with diseases of the skin (urticaria and angioneurotic edema) and, of course, patients with exophthalmic goiter. It may be significant that none of those with increased blood pressure (over 140, with or without renal lesions) are found above the normal maximal range of 11.5.

When we examine tables 6 and 7, with the results of examinations in twenty of the extreme cases, several differences become apparent. The relation to permeability of the capillaries and blister time is, of course, obvious. The group of persons with the low inflammatory indexes are much older, their calcium levels are higher, their K/Ca ratios are lower, their Kromayer light erythema times and their ice reaction times are longer and their flares due to epinephrine and wheals due to thyroxin are larger.

There are proportionately more sympatheticotonic persons among those with low than among those with high indexes, despite the fact that persons with cardiovascular renal lesions are found more frequently at the low end of the scale.

CALCIUM, POTASSIUM AND K/CA RATIO

The relation of the calcium and the potassium and the K/Ca ratio of the blood serum of normal persons, as well as of patients ill from various diseases, has been studied with considerable interest in recent years. The relations to the autonomic reactions, in particular, have received much attention. Kylin,⁵ as well as the Kraus school, showed definite relations to asthma⁶ and hyperpiesis.⁷

In the previously published results of examinations of "normal" persons, no evidence was presented as to their actual physical normalcy. In our group of 100 "normal" men, only twenty could actually be as classified. The remaining eighty showed evidence of cardiovascular renal abnormality, healed or active tuberculosis, syphilis, etc.

5. Kylin, E.: *Acta med. Scandinav. (suppl.)* 1:112, 1927.

6. Kylin, E.: *Klin. Wchnschr.* 6:1742, 1927.

7. Kylin, E.: *Zentralbl. f. inn. Med.* 48:431, 1927.

Our determinations were made on fresh serum with the Clark-Collip method for calcium and the Kerr modification for potassium. The results have been tabulated in table 8.

Chart 4 may aid in making the conditions more apparent. It will be noticed that the K/Ca curve commences with a low ratio of 1.12 in a young man (no. 132) 25 years of age (whose interesting series of clinical manifestations of disease we have described on page 220) and reaches a high ratio of 3.22 in a man 52 years of age (no. 93), who has had hay-fever each fall, is sensitive to halibut, shows x-ray evidence of myocarditis and is short of breath on exertion.

When we analyze the K/Ca ratios of the so-called normal group of 100, several interesting relations are to be observed.

Normal Persons.—In the first place, the actually normal persons fall, with two exceptions, within the range from 1.7 to 2.4. One of the two exceptions, with a ratio of 1.53, gives a markedly vagotonic reaction to epinephrine. The other, with a ratio of 2.9, is apparently healthy in every respect.

Persons with Roentgenologic Evidence of Healed Parenchymal Tuberculosis and Syphilis.—Of the seventeen persons with roentgenologic evidence of healed parenchymal tuberculosis, who are otherwise normal, eleven fall within the normal range, while seven of the nine syphilitic persons are also included within these limits. Tuberculosis, unless active, and syphilitic infection apparently do not materially alter the status.

Persons with Active Tuberculosis.—When one now turns to the group with roentgenologic evidence of active tuberculosis, one meets an interesting change. The average ratio for the entire group is 2.08, i. e., normal, but inspection of the chart will reveal that the ratios in the active cases are all outside the normal limits. Five persons have low ratios. Of these, one has albuminuria. These five all have low or normal blood pressure. The other five are at the extreme opposite end, with high K/ca ratios. Three of these have increased blood pressure, one normal blood pressure with albuminuria and the fifth a history of angioneurotic edema.

Persons with Cardiovascular Renal Lesions.—The persons with cardiovascular renal lesions are found scattered over the entire range of the K/Ca ratio without any apparent relation to blood pressure, to the degree of sclerosis of the larger vessels (made apparent on roentgen examination) or to capillary changes. There are no true cases of primary hypertension in the group, there being only some with an increase in blood pressure of from 140 to 170 (without changes in the kidneys),

TABLE 8.—*The K/Ca Ratios, the Potassium Values and the Calcium Values of One Hundred So-Called Normal Persons, as Well as of Patients with Glaucoma, Exophthalmic Goiter, Etc.*

Individual Number		K/Ca Ratio	Calcium, Potassium,	
			Mg.	Mg.
132	Eczema sensitized	1.12	13.4	15
46*	Inanition; worry	1.24	13.8	17.4
86*	Inanition; previous angioneurotic edema.....	1.20	12.6	15.9
62*	Aortic regurgitation	1.2	12.2	15.2
133	Scleroderma	1.32	13.2	17.5
90*	Nervous	1.34	11.4	14.3
110*	Edema under eyes; roentgenographic evidence of healed tuberculosis	1.34	12.1	16.3
113	Arthritis; possibly tuberculosis of lungs.....	1.4	13.2	17.2
88*	Roentgenographic evidence of active tuberculosis.....	1.4	9.4	13
112*	Roentgenographic evidence of arteriosclerosis.....	1.4	12.6	18
171	Menstrual urticaria	1.4	12.06	17.9
173	Cord tumor; worry	1.43	12.7	18.7
174†	Normal (vagotonic reaction to epinephrine).....	1.43	12.7	18.2
77*	Previous sensitization	1.44	10.8	15.6
70*	Arthritis deformans; arteriosclerosis; nephritis.....	1.45	11.4	16.6
15*	Healed tuberculosis	1.46	14.5	21.2
108*	Roentgenographic evidence of active tuberculosis, chronic	1.47	10.4	15.3
3*	Healed tuberculosis; nervous.....	1.47	11.1	16.7
45*	Increased blood pressure; (had nephritis as a result of scarlet fever)	1.48	11.2	16.6
130*	Nephritis; arteriosclerosis	1.49	10.4	15.5
109	Nervous; worry	1.5	10.8	16.1
82*	Increased blood pressure; changes in capillaries.....	1.5	11.4	17.2
22	Exophthalmic goiter	1.5	12.1	18.2
20*	Roentgenographic evidence of active tuberculosis.....	1.53	11.4	17.4
134*	Increased blood pressure; nephritis.....	1.56	9.9	15.6
60	Increased blood pressure; changes in capillaries.....	1.56	11.4	17.5
15*	Healed tuberculosis	1.55	12.1	18.8
111*	Arteriosclerosis; old syphilis.....	1.55	11.8	18.3
145	Changes in capillaries; glaucoma; arthritis; syphilis...	1.55	10.1	15.7
42*	Myocarditis	1.56	11.4	17.8
146	Myasthenia gravis; idiosyncrasy.....	1.56	9.2	14.4
100	Sensitized; healed tuberculosis; Buerger's disease; syphilis	1.56	12.34	10.24
102*	Roentgenographic evidence of active tuberculosis.....	1.63	10.6	17.3
172	Sensitized; Raynaud's disease; healed tuberculosis.....	1.64	13	21.3
129*	Roentgenographic evidence of active tuberculosis; nephritis	1.65	11.5	19
135	Nervous; healed tuberculosis; nephritis.....	1.65	11.9	19.6
69	Nervous; increased blood pressure; ulcer; healed tuberculosis	1.66	9.6	16
65*	Nephritis; changes in capillaries.....	1.67	9.8	16.4
106*	Dilatation of aorta.....	1.69	11.2	19
127*	Nephritis; healed tuberculosis.....	1.68	9.7	16.2
131	Exophthalmic goiter	1.7	10.6	18
80*	Nervous; changes in capillaries; healed tuberculosis; previously sensitized	1.7	8	13.7
40*	Changes in capillaries.....	1.73	10.8	18.7
72†	Normal	1.73	10.8	18.7
73*	Positive Wassermann reaction.....	1.74	11.2	19.5
143	Pellagra; syphilis	1.74	9.7	16.9
149	Nervous; worry	1.74	10.1	17.4
14*	Nephritis; sensitized	1.75	11.2	19.6
44†	Normal	1.76	10	17.6
75*	Increased blood pressure	1.78	10.8	19.2
79*	Increased blood pressure; ulcer; changes in capillaries.....	1.78	11.2	20
84*	Albuminuria; changes in capillaries.....	1.78	10	17.8
150	Glaucoma; healed tuberculosis; hyaline casts.....	1.78	12	21.3
165	Glaucoma; dilated aorta; nephritis.....	1.79	10	17.96
144	Pellagra; changes in capillaries.....	1.79	9.8	17.6
117	Syphilitic arthritis	1.8	9.2	17.5
85*	Slight fever, unknown origin.....	1.8	10.6	19.1
74*	Changes in capillaries.....	1.8	11	19.9
6	Nephritis; arteriosclerosis; myocarditis.....	1.8	10.5	18.9
4†	Normal	1.8	11.8	21.2
89*	Healed tuberculosis	1.81	9.2	16.7
105*	Healed tuberculosis	1.81	9	17.1
122†	Normal	1.81	10.6	19.2
60*	Arteriosclerosis; myocarditis; hyaline casts.....	1.82	11	20
113*	Arteriosclerosis; healed tuberculosis.....	1.82	10.2	18.6
63*	Arteriosclerosis; healed tuberculosis.....	1.83	11.4	20.9
126	Exophthalmic goiter	1.83	9.8	18.3
64†	Normal; slightly nervous.....	1.84	9	16.6
90*	Healed tuberculosis	1.86	9.6	17.9
76*	Nephritis; dilated aorta; granular casts.....	1.87	10.8	20.2
103*	Arteriosclerosis; myocarditis	1.88	9.2	17.3
136	Pellagra; arteriosclerosis; changes in capillaries.....	1.88	10	18.8
138	Fröhlich syndrome (?); myocarditis (?).....	1.88	10.6	19.9

* Indicates that the person is one of the group of 100 so-called normal persons.

† Indicates that the person is apparently normal on examination.

‡ Changes in capillaries means increased dilatation or actual granulation and tortuosity.

§ Blood pressures of 140 or over are noted as increased.

TABLE 8.—*The K/Ca Ratios, the Potassium Values and the Calcium Values of One Hundred So-Called Normal Persons, as Well as of Patients with Glaucoma, Exophthalmic Goiter, Etc.—Continued*

Individual Number		K/Ca Ratio	Calcium, Potassium,	
			Mg.	Mg.
168	Orthostatic albuminuria	1.88	9.4	17.7
43*†	Normal	1.89	9.2	19.4
164	Nephritis; glaucoma; syphilitic aortitis.....	1.89	8.7	16.54
139	Urticaria; vitiligo; changes in capillaries.....	1.9	9.7	18.4
167	Glaucoma; arteriosclerosis; changes in capillaries.....	1.9	12	22.72
16	Exophthalmic goiter; healed tuberculosis; changes in urine	1.9	11.4	21.6
39*	Syphilis	1.91	9.4	18
98*	Arteriosclerosis	1.93	8.8	17
128*	Arteriosclerosis; healed tuberculosis; albumin; changes in capillaries	1.93	10.2	19.7
68*	Healed tuberculosis	1.94	8.8	17.1
116	Urticaria	1.94	10	19.4
59*†	Normal	1.95	9.6	18.8
115*	Arteriosclerosis; albumin	1.95	7.8	15.2
142	Neoplasm (syphilis); arteriosclerosis.....	1.95	9.4	18.3
180	Neoplasm (mole)	1.96	11.11	21.56
161	Glaucoma; albumin; changes in capillaries.....	1.96	9.7	18.03
160	Glaucoma; healed tuberculosis; asthma.....	1.96	10.86	21.6
120	Purpura; changes in capillaries.....	1.99	10	19.9
174	Raynaud's disease ?	2	10.8	21.5
158	Hodgkin's disease	2	9.33	18.53
147	Epidemic encephalitis	2	9.8	19.7
71*	Arteriosclerosis	2	8.8	17.5
67*	Dwarf	2	8.8	17.6
52*	Healed tuberculosis	2	10.4	20.9
8*†	Normal	2	10.5	21
1	Nervous	2	12.1	24.9
2	Epilepsy; angioneurosis	2	12.9	26.1
9	Exophthalmic goiter; changes in capillaries.....	2.04	11.5	23.5
152	Angioneurotic edema; hyaline casts.....	2.05	9.8	20.1
101*	Healed tuberculosis; eczema	2.06	9.4	19.4
96*	Arteriosclerosis	2.07	8.2	17
94*†	Normal	2.08	8.4	17.5
153	Glaucoma; nephritis; healed tuberculosis.....	2.08	9	18.7
119	Adenoma of thyroid.....	2.1	9	18.7
24*	Healed tuberculosis	2.12	11.7	24.8
27	Syphilis; lead poisoning.....	2.14	10	21.4
39	Angioneurotic edema; changes in capillaries.....	2.14	9.8	21
58	Exophthalmic goiter	2.15	12	25.9
5	Healed tuberculosis	2.16	11.9	25.7
41*†	Normal	2.16	9.8	21.2
36*	Albuminuria	2.17	12.1	26.3
123	Carcinoma of thyroid; arteriosclerosis.....	2.17	9.2	20
159	Exophthalmic goiter	2.17	8.23	17.9
23*	Healed tuberculosis	2.19	13.1	28.6
28*	Healed tuberculosis	2.17	11	24.1
170	Diabetes, etc.; glaucoma; increased blood pressure....	2.2	10.6	23.71
11	Exophthalmic goiter; healed tuberculosis.....	2.21	10.9	24.1
78*†	Normal	2.23	8.4	18.8
137	Glaucoma; albuminuria	2.24	8.1	18.2
37*†	Normal	2.26	10	22.6
121	Increased blood pressure; arthritis deformans.....	2.27	8.9	20.2
166	Eosinophilia of unknown origin.....	2.27	9.1	20.66
49*	Hyaline casts	2.29	11	25.2
107*	Arteriosclerosis; myocarditis	2.3	8	18.4
83*†	Normal	2.3	8.2	19
87*†	Normal	2.32	8.4	19.5
92*	Neurosis	2.32	8.4	19.5
30*	Arteriosclerosis; increased blood pressure.....	2.33	10.3	24
61*	Arteriosclerosis; changes in capillaries; albuminuria....	2.35	7.6	17.6
97*†	Normal (nervous)	2.37	8.4	20.9
100*	Healed tuberculosis	2.38	9	21.5
29*†	Normal	2.39	10	23.9
114*	Tuberculosis; arteriosclerosis; nephritis.....	2.4	8	19.2
50*†	Normal	2.4	11.4	27.4
10*	Healed tuberculosis	2.4	10.1	24.6
96*	Healed tuberculosis	2.41	7.8	18.8
13*	Healed tuberculosis	2.48	9.6	23.8
148	Glaucoma; vitiligo; arteriosclerosis.....	2.5	9.7	24.3
47*	Healed tuberculosis	2.51	10.4	26.2
21*	Albuminuria; changes in capillaries.....	2.51	10.2	25.6
56*	Tuberculosis; has had angioneurotic edema.....	2.52	9.8	26.6
51	Exophthalmic goiter	2.58	10	25.8
25*	Tuberculosis; albuminuria	2.6	11.1	28.8
140	Glaucoma; tuberculosis; sensitized.....	2.61	11.4	29.7
26*	Syphilis	2.61	10.2	26.6
33	Epileptic	2.73	9.5	26.1
32*	Increased blood pressure.....	2.73	9.5	26.1
48*	Syphilis	2.87	9.0	27.6
34*	Changes in capillaries.....	2.89	9.0	27.7
35*†	Normal	2.9	8.7	25.2
81*	Arteriosclerosis; myocarditis; pruritis.....	3.07	8.4	25.8
104*	High blood pressure; tuberculosis; arteriosclerosis....	3.09	7.4	22.9
55*	Albumin and hyaline casts; healed tuberculosis.....	3.1	8	24.9
93*	Sensitized; myocarditis	3.2	7.6	24.5



Chart 4.—The K/Ca ratio of normal persons and patients with various clinical conditions (indicated by heavy line). Individual identification marks at bottom are included in the group of 100 "normal" men.

but these are all in persons of advanced age. With one exception, the members of this group all have sthenic hearts.

"Nervous" Persons.—The so-called nervous group seems, without doubt, to be associated with changes in the K/Ca ratios. One must, however, consider the possibility that the changes in the ratios are secondary to the nervous conditions rather than the cause of these. Perhaps some of the symptoms (feeling of weakness, etc.) may be sought in an alteration of the salt balance. These cases include the following:

CASE 86.—A former dentist, American, 50 years of age, had always been the most nervous one of his family. A sister had exophthalmic goiter. The patient had an attack of angioneurotic edema when a dental student. He used alcohol excessively. The death of a child precipitated a "breakdown." He lost his practice and his family, and became "down and out." He worked occasionally as a janitor.

It may be noticed that the sugar and the globulin were increased, the total protein was low, the muscle reactivity was increased and the reaction to epinephrine hydrochloride was vagotonic. The weight/length ratio was diminished.

CASE 90.—A mail sorter, 30 years of age, complained that since the year previously he got "rattled" easily and was nervous. He was extremely sensitive to venipuncture. The family history was negative. The patient reacted markedly to epinephrine with a tremor and a feeling of discomfort. The weight/length ratio was diminished. The intracutaneous reactions to morphine and epinephrine (the flare) were increased; those to thyroxin were diminished. The capillaries of the skin were reduced in number.

CASE 173.—A highly successful and intelligent American business man, 40 years of age, with cord tumor, had suffered from incidental worry for two years. The family history was negative other than that the mother was nervous and died from tuberculosis.

The K/Ca ratio in December, 1927, was 1.57 (calcium, 13.5; potassium, 21.3). The K/Ca ratio in May, 1928, was 1.43 (calcium, 12.7; potassium, 18.17). The sugar was 80, the globulins were diminished, the skin resistance was low, the blood pressure was low and the pulse rate was high. The patient reacted strongly to epinephrine. The weight/length ratio was diminished. The intracutaneous reactions to epinephrine were increased; flares due to morphine, thyroxin and caffeine were absent.

CASE 3.—A highly intelligent Jewish chemist, 25 years of age, had been nervous for several years. The father suffered from Raynaud's disease.

The patient's reaction to epinephrine was vagotonic. The weight/length ratio was normal. The intracutaneous reactions to thyroxin and caffeine (wheals and flares) were diminished.

CASE 109.—An American spinster, 42 years of age, spent much of her time in bed because of "weakness." She had a unilateral ovariectomy fifteen years previously. She menstruated normally. She complained of palpation, nervousness, weakness and excessive perspiration. One sister had an exophthalmic goiter. The mother, 72 years of age, was nervous, with a blood pressure of 160.

The reaction to epinephrine was slightly sympathetotonic, the weight/length ratio low (140), the skin reactions to ice and the Kromayer light faint and the intracutaneous reactions to thyroxin (flares) increased.

CASE 135.—A Jewish tailor, 26 years of age, was nervous. The mother died of "shock" following an air raid during the war. The patient had lost 15 pounds (6.8 Kg.) during the last year. The reaction to epinephrine was vagotonic. The weight/length ratio was low. The urine showed granular casts. The capillaries of the skin showed granulations. A healed parenchymal tuberculosis was revealed by the x-rays. The globulins were increased. The pharmacologic skin reactions to epinephrine and morphine (wheals and flares) were reduced; the wheals due to thyroxin and caffeine were increased, and the flares were absent.

CASE 69.—A Jewish medical student, 22 years of age, alert and intelligent, had a duodenal ulcer and was nervous. He had an occasional tremor. His blood pressure was increased. The mother was nervous and had high blood pressure (210); the father was nervous and had high blood pressure (175). The patient felt weak when blood was drawn. He gave a marked reaction to epinephrine; he felt ill, had a headache and turned pale, and the vascular reaction was markedly sympathetotonic. The weight/length ratio was low. The pharmacologic skin reactions to epinephrine and thyroxin (wheals and flares) were increased; the wheal due to caffeine was increased.

CASE 80.—An American electrician, 30 years of age, was nervous and had a tremor. He became nervous in 1924 after an explosion in a salt mine. He had urticaria in 1922.

The reaction to epinephrine was not marked. The reaction to the Kromayer light was marked and the capillary permeability was high. The resistance of the skin to electric current was high. The weight/length ratio was normal. All flares due to the pharmacologic substances employed in the intracutaneous injections were increased. The wheal due to epinephrine was diminished and that from thyroxin was increased. The capillaries of the skin showed beginning granulations.

CASE 149.—An American plumber, 35 years of age, had had financial reverses, and was nervous and sleepless. The family history was negative, except for tuberculosis.

The reaction to epinephrine was not marked. The Kromayer light erythema time was shortened, the skin resistance was high and the weight/length ratio was relatively low. The serum globulins were practically absent. The pharmacologic skin reactions to epinephrine were negative, the flares due to other intracutaneous injected substances were reduced or absent and the wheal due to thyroxin was increased.

CASE 1.—A Jewish medical student, 23 years of age, who had a "nervous breakdown" a year before examination, felt weak and had a tremor.

The reaction to epinephrine was marked, the sugar was increased and the Kromayer light, ice and blister reactions were delayed. The weight/length ratio was low. The intracutaneous injection of epinephrine hydrochloride and morphine left the skin unchanged; the wheal and the flare due to thyroxin were increased.

CASE 92.—A Jewish medical student, 23 years of age, was nervous and unable to concentrate, and had a feeling of weakness and an occasional tremor. He had bowel movements once or twice a week; he sweat easily. The father died from hypernephroma; the mother had periarteritis nodosa (?). The reaction to epinephrine was marked. The blister time and ice reaction were delayed. The

reaction to the Kromayer light was faint. The skin resistance was increased. The weight/length ratio was normal. The intracutaneous reactions to epinephrine and morphine were normal. Those to thyroxin were increased.

The K/Ca Ratio.—In a previous examination of this material in its relation to the vascular reaction to epinephrine⁸ it was found that a small group of outstandingly sympatheticotonic persons had low K/Ca ratios as compared with the vagotonic ones. We mentioned, however, that many exceptions were observed.

It is apparent that certain disturbances closely associated with a vascular supply are definitely associated with an alteration of the K/Ca ratio. These manifestations take the form of lesions of the skin, lesions of the gastro-intestinal tract, respiratory diseases (hay-fever, asthma, etc.), glaucoma, etc. A change of the K/Ca ratio may influence the permeability of the endothelial cells, which would result in instability and a probable tendency to sudden alterations producing not only edema but other local disturbances of cell function with pruritis, sclerosis, atrophy, etc. Such a change may also involve the contractile mechanism of the vessels including both capillary and arteriole and arterial elements, through the autonomic nervous supply.

It seems probable that the higher centers may play a rôle in this vegetative reorientation. Our results make it evident that the majority of the so-called nervous persons have a low ratio. In this change, the calcium is less involved than the potassium; the calcium may range from high to normal, but the potassium is usually found to be low.

We have the impression that this may result from mental disturbances. It is difficult, however, to determine whether mental disturbances precede the change in the chemical blood picture or follow as a result of it. Tómasson,⁹ in a series of carefully conducted examinations of persons with psychic disturbances, found that the K/Ca ratio showed alterations before the onset of the mental upset. Certainly, a mere examination of the calcium is insufficient to supply us with the necessary information. In view of the close connection between the mental state and the functioning of certain of the endocrine glands, the change in the K/Ca ratio with change in the mental condition should not surprise us.

It seems probable that it is the abnormality of the ratio rather than its change in any one direction that brings about functional vascular disturbances and with this certain manifestations of disease. Thus, one

8. Petersen, W. F.; Levinson, S. A., and Arquin, S.: The Relation of the Reaction to Epinephrine to the Potassium-Calcium Ratio and Other Ratios, *Arch. Int. Med.* **42**:256 (Aug.) 1928.

9. Tómasson, H.: *Blodets Elektrolyter, etc.*, Copenhagen, Levin & Mungsgaard, 1927.

may examine the history of two persons who are, respectively, at the bottom and the top of the K/Ca scale.

CASE 132.—A medical student, 26 years of age, alert and intelligent, had a K/Ca ratio of 1.12. He was the son of a physician. When 12 years of age, he had severe attacks of hyperacidity and dizziness with vomiting. These attacks would occur intermittently several times a month and usually lasted a day; they were relieved by food. The attacks became milder until 1918; then they became more severe. He was free from them at the time of examination. In 1919, he had a severe attack of hiccup, which lasted for forty-eight hours. From 1918 to 1921, he was bedridden with tuberculosis of the right lung. During the course of the tuberculosis, he suffered severely from night sweats. He had hay-fever from the time that he was a young boy until 1919, when it disappeared, and at various times in 1918 he suffered from urticaria. In 1920, he had influenza, associated with a mastoiditis. Since 1919, he had had ulcerative colitis with the possibility of a duodenal ulcer. For one week in 1919, he had diabetes insipidus. During the past three years, he had had hypo-acidity. At the time of examination he was apparently well, except for chronic eczema in both hands. Physical examination revealed no marked changes.

The x-ray picture of the chest was practically negative. However, he had an eosinophilia of from 10 per cent to 14 per cent, and stated that he had never been able to alkalinize the urine, despite large doses of bicarbonate.

CASE 93.—An American laborer of Irish extraction, 53 years of age, rather alert, intelligent and somewhat irritable, had a K/Ca ratio of 3.2. He had always done heavy work. He was a periodic drinker until four years before. He had had hay-fever and asthma all of his life. He was attacked by these in the fall, and he stated that he was sensitive to ragweed. For the past fifteen years, he had been sensitive to halibut. X-ray examination revealed evidence of a myocarditis, and he complained of shortness of breath. The family history was apparently negative.

Calcium.—The lowest amount of serum calcium, 7.4 mg. per hundred cubic centimeters, occurs in a patient (no. 104) with roentgenologic evidence of active tuberculosis and a coincident high blood pressure; the largest amount, 14 mg. per hundred cubic centimeters, occurs in a patient with healed parenchymal tuberculosis. The actually normal group have a range of calcium values from 8.2 to 12.7 mg.

In Table 9, some of the observations on the twenty persons having the highest levels of calcium (averaging 12.7 mg. per hundred cubic centimeters) have been tabulated. The corresponding observations on the persons with outstandingly low levels of calcium are tabulated in table 10. In order to facilitate comparison, table 11 brings together the averages for the group with high levels of calcium, the group of 100 "normal" men and the group with low levels of calcium.

In chart 5, the normal ranges of the calcium levels are presented. The persons with healed tuberculosis are more frequently in the normal range or the high range, while those with roentgenologic evidence of active tuberculosis are scattered. There appears to be no correlation of these conditions with the cardiovascular condition.

TABLE 9.—The Results of Examinations of the Twenty Persons with the Highest Levels of Serum Calcium

Individual Number	Diagnosis	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure { Systolic Diastolic }	Pulse Rate	Permeability of Capillaries
18	Healed tuberculosis	58.4	70.2	2	1	10	Vagotonic	120 80	88	70
40	Inanition.....	56.2	61	2	1.70	15	Sympatheticotonic	21.2	12.2	140 82	76	50
132	Eczema.....	40.3	67	...	0.31	10	Vagotonic	18.4	13.6	132 78	56	68
133	Scleroderma.....	50.2	77	...	0.70	30	Sympatheticotonic	92 68	96	..
23	Healed tuberculosis	57.4	85	3	0.42	28	Vagotonic	17.2	7.2	105 58	82	67
172	Raynaud's disease..	76	...	0.08	45	Sympatheticotonic	22.4	15	108 78	94	72
2	Epilepsy.....	55.6	74	...	0.10	..	Sympatheticotonic	100 68	100	60
173	Worry.....	55.7	80	...	0.09	15	Sympatheticotonic	21	18	106 68	92	57
17	Normal.....	59.1	61.5	6	0.22	20	Vagotonic	20.8	20.6	130 70	60	66
86	Nervous.....	55	94	1.4	0.36	25	Vagotonic	18.8	15.4	119 60	74	58
171	Urticaria.....	48.7	72	...	0.08	20	Sympatheticotonic	17.5	18	114 60	95	73
112	Arteriosclerosis....	57	68	2.4	2.70	19	Vagotonic	22.4	9.8	130 80	75	54
160	Buerger's disease..	55.1	67	...	0.23	25	Sympatheticotonic	20.8	18	118 78	82	62
62	Aortic regurgitation	56.8	67	5	0.15	15	Vagotonic	17.2	11.4	140 40	64	52
118	Chronic arthritis; pcurisy	54.2	80	2.8	1.90	12	Vagotonic	10.8	12	120 60	72	87
127	Nephritis.....	59.1	81	3	1.20	16	Sympatheticotonic	18.4	15.4	106 76	86	80
110	Healed tuberculosis	57.2	61	2	0.60	30	Vagotonic	20.8	12	110 62	84	54
22	Exophthalmic goiter	52	91	3	0.17	5	Sympatheticotonic	26.4	5	144 74	92	73
15	Healed tuberculosis	57.6	70	6	0.10	38	Sympatheticotonic	23.2	11.6	128 68	60	68
1	Nervous.....	62.1	113	...	0.11	25	Sympatheticotonic	20	13.2	132 74	80	66
Averages and totals....		56.2	75.7	3.2	0.61	21	9 V., 11 S.	20.2	13.6	120 69	80	64

TABLE 10.—The Results of Examinations of the Twenty Persons with the Lowest Levels of Serum Calcium

Individual Number	Diagnosis	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure { Systolic Diastolic }	Pulse Rate	Permeability of Capillaries
104	Tuberculosis; arteriosclerosis	57.2	55	1.2	0.08	25	Vagotonic	20.8	12	176 100	84	54
98	Myocarditis; hay-fever	57	70	2.4	0.25	12	Vagotonic	20.4	10	113 71	86	50
61	Arteriosclerosis....	53.1	72	7.4	0.28	7	Vagotonic	19.6	13.4	142 82	64	70
96	Healed tuberculosis	61.0	77	1.6	0.39	10	Sympatheticotonic	23.6	12	110 66	68	50
115	Arteriosclerosis....	51.8	60	2	0.28	10	Vagotonic	17.2	14.2	148 84	84	46
56	Nephritis.....	56.6	73	0.6	0.39	20	Vagotonic	17.6	11.2	128 68	84	60
80	Nervous.....	53.2	69	3.8	1.6	30	Vagotonic	14.8	13.4	116 68	64	91
114	Tuberculosis.....	60.6	75	4	0.14	25	Sympatheticotonic	20.4	12	174 60	48	64
107	Myocarditis; arteriosclerosis	55.2	60	2.8	0.33	15	Vagotonic	20.8	13.4	134 72	72	58
137	Glaucoma.....	51.9	73	0.8	1.90	30	Vagotonic	15.4	13	119 67	78	61
83	Normal.....	53.1	68	4	0.16	20	Vagotonic	17.2	13.4	114 64	60	51
96	Arteriosclerosis....	53.4	77	1.6	0.11	40	Vagotonic	18	12.4	140 85	68	57
159	Exophthalmic goiter	54.8	71	...	0.22	7	Sympatheticotonic	25	12	132 68	76	60
81	Myocarditis; arteriosclerosis	57	63	2.3	0.10	45	Vagotonic	14	10	144 63	76	59
97	Normal.....	57.2	60	4.5	0.22	20	Sympatheticotonic	19.2	12	100 62	68	54
92	Nervous.....	56.8	67	2.9	0.57	20	Sympatheticotonic	20.4	15.2	110 60	72	82
87	Normal.....	55.4	94	3.5	0.42	18	Sympatheticotonic	16	12	104 62	70	56
78	Normal.....	62.7	67	1	0.62	10	Sympatheticotonic	19.6	12.4	122 70	74	86
35	Normal.....	57.6	79	1.8	0.28	20	Vagotonic	22.8	9.2	108 78	62	54
164	Syphilis; glaucoma	55.6	65	...	0.23	15	Vagotonic	18	110 75	80	71
Averages and totals....		56.1	69.7	2.6	0.43	19.3	13 V., 7 S.	19	12.3	127 71	82	62.6

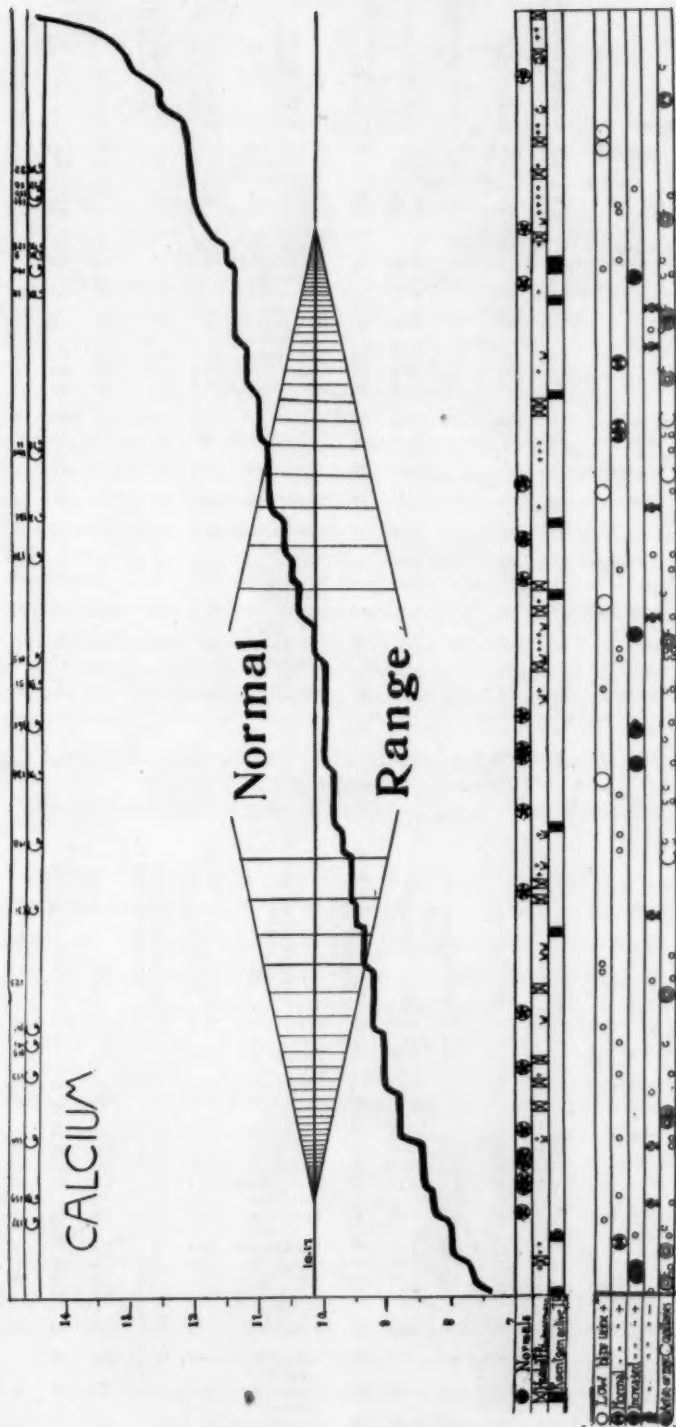


Chart 5.—The calcium level in the serum of normal persons and patients with various clinical conditions.

The groups with high levels of calcium include none of the persons having active tuberculosis, but include a number of persons with skin disorders, as well as those with peripheral vascular changes—scleroderma, Raynaud's disease, Buerger's disease, etc. A number of outstandingly sympathetotonic persons are included, but vagotonic types also occur.

In general, the carbon dioxide tension is reduced; the sugar, the skin resistance, the pulse rate, the wheals due to epinephrine and thyroxin and the permeability of the capillaries are increased; the ice reaction time is prolonged, and the blood pressure is lower than in the group with low levels of calcium.

The group with low levels of calcium, on the other hand, includes two persons with active tuberculosis, an increased number of arterio-

TABLE 11.—*Comparison of the Averages Obtained for the Groups Showing High Levels and Low Levels of Calcium with the Averages Obtained for the Group of One Hundred Normal Men*

Group	Number in Group	Calcium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Pulse Rate	Ice Reaction Time, Seconds	Intracutaneous Reaction to		Systolic	Diastolic	Permeability of Capillaries
									Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)			
Group with high level of calcium.....	20	12.7	55.2	75.7	3.2	0.61	80	21	20.2	13.6	120	60	64
Group of "normal" men.....	100	10.17	57.7	71	3.2	0.46	72	19	19.2	11.2	124	71	62
Group with low level of calcium.....	20	8.1	56.1	69.7	2.6	0.43	72	19.3	19	12.3	127	71	62.6

sclerotic persons (as proved by roentgen examination), as well as more normal persons. There are, too, apparently more persons of the vagotonic type in this group, thirteen of the twenty giving such a reaction.

Potassium.—The highest potassium value, 29.7 mg. per hundred cubic centimeters, is found in a patient with glaucoma, hay-fever and roentgenologic evidence of active tuberculosis; the lowest 13.1 in a person with roentgenologic evidence of active tuberculosis. The range for the actually normal group is from 16.6 to 27.4.

In tables 12, 13 and 14, some of the observations on the group with high levels of potassium (averaging 26.5) are recorded. In table 13, the corresponding observations on the group with low levels of potassium (averaging 15.1) are recorded. For purposes of comparison, table 14 brings together the averages of the groups with the high levels of potassium, the group of 100 "normal" men and the group with low levels of potassium.

TABLE 12.—Results of Examinations of the Twenty Persons with the Highest Levels of Potassium

Individual Number	Diagnosis	Potassium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Thyroxin, Wheal (Diameter, Mm.)	Epinephrine, Wheal (Diameter, Mm.)	Blood Pressure Systolic Diastolic	Permeability of Capillaries	Inflammatory Index	
140	Glaucoma; tuberculosis; sensitized	29.7	55.6	82	...	0.45	40	Vagotonic	18	27	100	70	68	4
25	Tuberculosis.....	28.8	59.8	67	1.2	0.24	20	Sympatheticotonic	21.2	9	140	80	57	9.5
23	Healed tuberculosis	28.6	57.4	85	3	0.42	28	Vagotonic	17.2	7.2	102	58	67	11.1
50	Tuberculosis.....	28.6	56.6	65	1	0.32	15	Vagotonic	17.2	13.4	124	88	61	10
141	Glaucoma.....	28.2	64.6	88	...	0.20	15	Vagotonic	17.4	10	118	78
34	Changes in capillaries	27.7	56.4	78	2.7	0.59	25	Vagotonic	18	7.2	134	78	56	7.7
48	Syphilis.....	27.6	58.3	71	1.6	0.10	35	Sympatheticotonic	19.2	8	104	72	66	9.7
50	Normal.....	27.4	64.9	..	2.8	0.48	15	Sympatheticotonic	24.8	10.4	128	70	71	8.8
26	Syphilis.....	26.6	63.4	69	2	0.28	35	Vagotonic	19.6	7.2	92	48	72	11
36	Albuminuria.....	26.3	57.6	90	2.8	0.11	20	Vagotonic	20.8	7.4	104	50	58	7.2
47	Healed tuberculosis	26.2	56.4	72	5	0.13	15	Vagotonic	21.6	9	136	64	62	12.8
32	Arteriosclerosis.....	26.1	54.1	76	7.4	0.18	25	Vagotonic	23.6	9.8	144	80	60	10
33	Epilepsy.....	26.1	54.5	83	2	1.75	12	Sympatheticotonic	20	5.4	122	60	73	10
2	Epilepsy.....	26.1	55.6	74	...	0.10	..	Sympatheticotonic	100	68	69	9.8
58	Exophthalmic goiter	25.9	52.9	120	...	0.10	25	Vagotonic	19.6	11.2	124	60	75	15
81	Arteriosclerosis; myocarditis	25.8	57	68	2.3	0.10	45	Vagotonic	14	10	144	63	50	10
51	Exophthalmic goiter	25.8	55.5	91	5	0.13	..	Sympatheticotonic	19.2	9.2	124	50	77	14
5	Nervous.....	25.7	63.9	72	3.2	0.21	..	Vagotonic	132	92	72	13
21	Arteriosclerosis.....	25.6	62.9	72	3.9	0.74	25	Vagotonic	23.2	7.2	140	84	62	9
35	Normal.....	25.2	57.6	79	1.8	0.38	20	Vagotonic	22.8	9.2	108	78	54	6.7
Averages and totals...		26.5	58	75	2.9	0.35	24	14 V., 6 S.	20	9.8	121	70	65	10

TABLE 13.—The Results of Examinations of the Twenty Persons with the Lowest Levels of Potassium

Individual Number	Diagnosis	Potassium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure Systolic Diastolic	Permeability of Capillaries	Inflammatory Index	
88	Tuberculosis.....	13.1	58.1	79	2.5	0.68	15	Vagotonic	18.4	12.4	128	76	58	8.1
80	Nervous.....	13.7	53.2	69	3.8	1.60	30	Vagotonic	14.8	13.4	116	68	91	15.1
146	Myasthenia gravis.	14.4	71.00	77	...	0.55	30	Vagotonic	18	19	120	78	75	5
90	Nervous.....	14.5	57.9	68	...	0.44	10	Sympatheticotonic	18.4	6.2	122	54	60	7.6
132	Eczema.....	15	40.3	67	...	0.31	10	Vagotonic	18.4	13.4	132	78	68	11.3
62	Aortic regurgitation	15.2	56.8	67	5	0.15	15	Vagotonic	17.2	11.4	140	40	52	8.7
115	Arteriosclerosis.....	15.2	51.8	60	2	0.28	10	Vagotonic	17.2	14.2	148	84	46	5.7
108	Tuberculosis.....	15.3	54.1	68	0.6	0.44	18	Sympatheticotonic	18	14.8	94	52	63	8
134	Arteriosclerosis.....	15.4	54.8	71	...	0.68	12	Sympatheticotonic	23.6	19.2	148	86	60	4
130	Nephritis.....	15.5	55.6	86	2	0.35	15	20	11.2	106	..	71	4.7
77	Sensitized.....	15.6	60.6	71	1	1	35	Vagotonic	14	10	126	78	87	10
145	Glaucoma.....	15.7	55.4	70	...	0.35	20	Sympatheticotonic	18	16	136	80	67	4.4
86	Nervous.....	15.9	55	94	1.4	0.36	25	Vagotonic	18.8	15.4	118	60	58	3.8
69	Nervous.....	16	54.8	70	2	1.60	20	Sympatheticotonic	21.2	14.4	140	48	51	12.7
109	Nervous.....	16.1	51.4	67	...	0.47	25	Vagotonic	18	12	106	70	72	12
127	Nephritis.....	16.2	59.1	81	3	1.20	16	Sympatheticotonic	18.4	15.4	106	76	50	3.8
110	Healed tuberculosis	16.3	57.2	61	2	0.60	30	Vagotonic	20.8	12	110	62	54	7.2
65	Nephritis.....	16.4	53.1	65	0.4	0.80	13	Sympatheticotonic	15.8	9.2	100	70	61	10
64	Normal (nervous)..	16.6	55	52	5	0.22	7	Sympatheticotonic	20	6.4	112	60	66	10
45	Arteriosclerosis....	16.6	54.3	77	7.4	0.28	20	Vagotonic	20.4	16.4	162	114	54	9
Averages and totals...		15.1	55.2	70	2.7	0.63	18.5	11 V., 8 S.	18.4	13.1	123	70	63	8

In the group with the higher levels are three patients with roentgenologic evidence of active tuberculosis, two with syphilis, two with glaucoma and two with epilepsy. The reaction to epinephrine is predominantly vagotonic. The group with the low levels includes the "nervous" persons. In this group eleven react vagotonically.

As compared with the group having low levels of potassium the group having the high levels reveals higher Co_2 combining power, more sugar, larger wheals due to epinephrine, smaller wheals due to thyroxin and a higher inflammatory index. The reaction to ice is delayed.

TABLE 14.—Comparison of the Averages Found for the Groups with High and Low Levels of Potassium with the Averages Found for the Group of One Hundred "Normal" Men

	Number in Group	Potassium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure		Permeability of Capillaries	Inflammatory Index
Group with high level of potassium	20	26.5	58	75	2.9	0.35	24	14.2	30	9.8	121	70	65	10
Group of "normal" men.....	100	20.4	57.7	71	3.2	0.46	19	19.2	11.2	124	71	62	8.2
Group with low level of potassium	20	15.1	55.2	70	2.7	0.63	18.5	11.2	18.4	13.1	123	70	68	8

SUMMARY AND CONCLUSIONS

An examination was made of the serum calcium and potassium of 100 so-called normal persons. Of this group, twenty were regarded as actually normal on careful examination.

The K/Ca ratio from 1.7 to 2.4 we regard as normal. Persons with roentgenologic evidence of active tuberculosis are at the extreme ends of the scale. Those with vascular changes in addition to the tuberculosis have the higher ratios. Among abnormal persons, glaucoma and exophthalmic goiter produce no marked deviations from normal. "Nervous" persons have low ratios.

The normal calcium range was found to be from 8.2 to 12.7. In the group with the high range are the persons with diseases of the skin, as well as those with peripheral vascular disturbances, such as scleroderma, Buerger's disease, Raynaud's disease, etc. These persons tend toward the sympatheticotonic type.

The normal potassium range extended from 16.6 to 27.4. The group with low levels of potassium includes the "nervous" persons.

TOTAL PROTEINS

Serum proteins for the normal as well as abnormal groups varied from a low of 6.33 per cent in patient 86 (nervous) to a high reading of 9.87 per cent in a case of so-called Buerger's disease (syphilitic). For the strictly normal group, the range was from 7.5 to 8.5 per cent. Patient 17, classified as normal, but with an abnormal K/Ca ratio, etc.,

TABLE 15.—*The Results of Examinations of the Twenty Persons with the Lowest Concentrations of Protein*

Individual Number	Protein, Mg.	Diagnosis	CO ₂ Combining Power	Weight/Length Ratio	Basal Metabolic Rate
86	6.33	Nervous.....	55	178	6.4
145	6.55	Glaucoma; syphilis.....	55.4	103	19
85	6.65	Fever, unknown origin.....	55.9	187	18.8
140	6.77	Tuberculosis; glaucoma.....	55.6
60	6.87	Cardiovascular renal condition.....	56.6	229
116	7	Urticaria.....	65.1	195	9
67	7	Dwarf.....	56.9	195	32
118	7	Tuberculosis; arthritis.....	54.2	154	-11
77	7	Sensitized.....	60.6	187	7.9
30	7.07	Arteriosclerosis.....	62.5	175	-6
139	7.10	Urticaria.....	50	176	5
123	7.16	Carcinoma of thyroid.....	52.4	263	48
110	7.20	Healed tuberculosis.....	57.2	190	49
11	7.20	Exophthalmic goiter.....	58.1	195	42
24	7.20	Healed tuberculosis.....	53.7	219	1
101	7.20	Eczema.....	57.4	191	31
92	7.20	Nervous.....	56.8	210	-1
96	7.26	Cardiovascular renal condition.....	53.4	243	31
132	7.30	Eczema.....	40.3	224	-1.2
161	7.30	Glaucoma.....	49.4	171	+16

TABLE 16.—*The Results of Examinations of the Twenty Persons with the Highest Concentrations of Protein*

Individual Number	Protein, Mg.	Diagnosis	CO ₂ Combining Power	Weight/Length Ratio	Basal Metabolic Rate
169	9.87	Buerger's disease.....	55.1	...	+7
164	9.56	Glaucoma; syphilis.....	55.6	223	-4.7
136	9.23	Pellagra.....	57.9	190	20
75	9.23	Cardiovascular renal condition.....	61.6	243	+2.5
56	9.14	Tuberculosis.....	56.6	247	-17.9
125	9.13	Exophthalmic goiter.....	55.5	197	59
170	8.92	Glaucoma.....	52.5	170	+38
5	8.92	Neurosis.....	6.39	210
32	8.80	Cardiovascular renal condition.....	54.1	190	+22
146	8.80	Myasthenia.....	71.06	192	+ 1.8
79	8.77	Ulcer.....	57	220	-15.2
17	8.72	Normal (?).....	59.1	216	-11
167	8.71	Glaucoma; arteriosclerosis.....	47.9	158	-13
117	8.71	Arthritis; syphilis.....	52.4	195	- 7
40	8.71	Changes in capillaries.....	55.7	201	22
154	8.71	Glaucoma.....	56.6	181	18
10	8.70	Healed tuberculosis.....	59.4	230	-12.4
68	8.66	Healed tuberculosis.....	51.1	217	25.8
121	8.66	Arthritis deformans.....	56.8	204	11
66	8.66	Cardiovascular renal condition.....	53.1	257	1.3

is again unusual in having a somewhat higher protein concentration, 8.75 per cent. We do not regard this as normal. The twenty persons with the lowest concentrations of the entire series are tabulated in table 15 (average, 7 per cent).

The twenty persons with the highest concentrations are presented in table 16 (average 8.9).

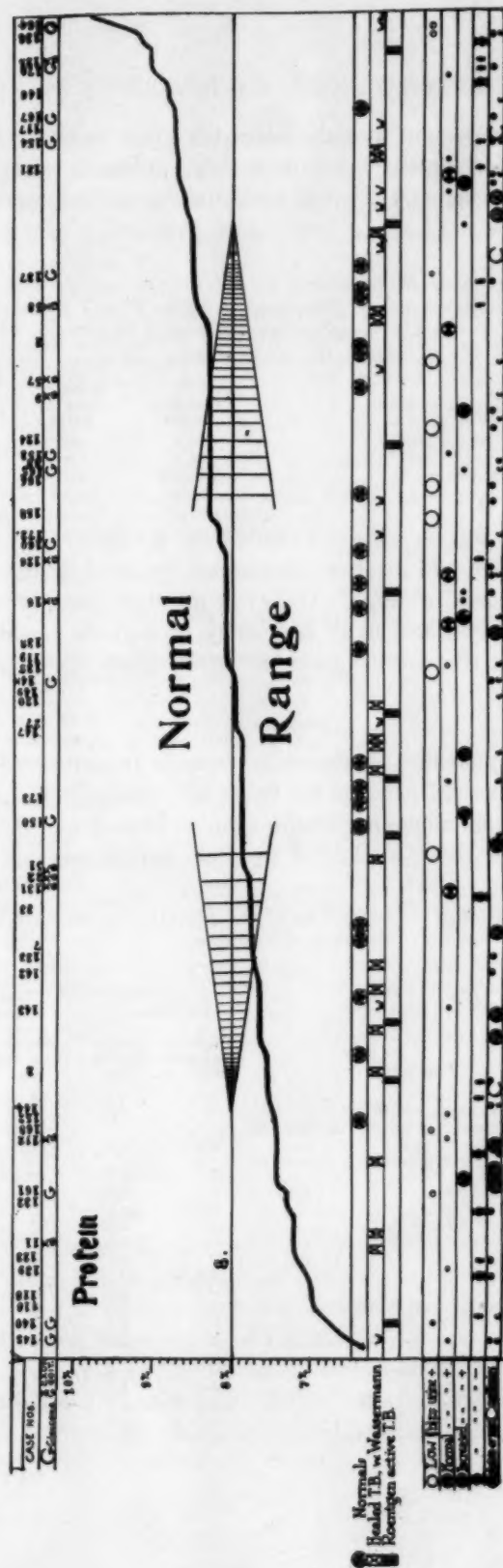


Chart 6.—The amount of protein in the serum of normal persons and patients with various clinical conditions.

A table of comparison with the normal is given in table 17. There are no obvious correlations other than those indicated, and these are by no means striking. A graphic presentation has been prepared in chart 6.

TABLE 17.—*Comparison of the Averages Found for the Groups with High and Low Concentrations of Protein with Those Found for the One Hundred "Normal" Men*

Group	CO ₂ Combining Power	Weight/ Length Ratio	Basal Metabolic Rate
Group with low level of protein.....	54.8	197	+15
Group of 100 "normal" men.....	57.7	217	+ 8
Group with high level of protein.....	57.1	210	+ 6

In general it will be observed that in the group of 100 "normal" persons, both active and inactive tuberculosis revealed by the x-rays is scattered over the entire range. The cases in which there were cardiovascular renal disturbances more frequently showed the higher concentrations. This is true of the cases in which glaucoma is present as well.

GLOBULINS

The range of globulins for the entire series is from 0 to 90 per cent. For the actually normal persons, the range is approximately from 20 to 45 per cent (with an albumin/globulin ratio of from 5 to 1.2). It may be noted from the curve in chart 7 that two normal persons (nos. 17

TABLE 18.—*The Results of Examinations of the Twenty Persons with the Lowest Amounts of Globulin*

Individual Num- ber	Glob- ulin	Diagnosis	Reaction to Epinephrine		Reaction to Thyroxin	
			Wheal, Diameter, Mm.	Flare, Radius, Mm.	Wheal, Diameter, Mm.	Flare, Radius, Mm.
149	0	Nervous.....	20	9.7	19	0
153	0	Edema; glaucoma; nephritis.....	22	6.5	18	0
144	2	Arteriosclerosis; pellagra; changes in capillaries.....	14.4	11.5	15	0
154	3	Arteriosclerosis; glaucoma; changes in capillaries.....	23	10	26	0
173	6	Cord tumor.....	21	12.5	18	0
166	8	Eosinophilia.....	17	11.5	18	0
138	11	Fröhlich's syndrome (?).....	23	9.5	17	6.5
108	13	Orthostatic albuminuria.....	18	16	14	0
150	15	Glaucoma.....	17	14	16	0
165	16	Glaucoma.....	16.8	13	12.5	0
17	17	Normal.....	20.6	10.2	20.6	10.4
49	17	Cardiovascular renal condition.....	12.4	10.2	4.2	1
158	17	Hodgkin's disease.....	19.2	11.3	23	0
69	17	Normal.....	22	7.2	15.6	8
139	18	Urticaria.....	16	11	14	12.5
25	19	Tuberculosis (x-ray evidence).....	21.2	12.2	9	15.2
142	19	Tumor of the brain.....	18.6	8.7	17	0
160	20	Buerger's disease.....	20.8	11	18	0
164	20	Glaucoma.....	18	14.7		
21	20	Cardiovascular renal condition.....	23.2	12.6	7.2	2.6

and 59) are slightly below and three (nos. 41, 29 and 43) are at the upper margin. Of these persons, no. 17 has been noted previously because of his deviations; of the three with high globulin, no. 29 has a trace of bile in the urine and no. 43 a decrease in the number of the capillaries of the skin.

TABLE 19.—*The Results of Examinations of the Twenty Persons with the Highest Amounts of Globulin*

Individual Number	Globulin	Diagnosis	Reaction to Epinephrine		Reaction to Thyroxin:
			Wheal, Diameter, Mm.	Flare, Radius, Mm.	Wheal, Diameter, Mm.
133	90	Scleroderma.....
115	60	Cardiovascular renal condition.....	17.2	6.2	14.2
130	60	Cardiovascular renal condition; arteriosclerosis.....	20	5.4	14.2
24	60	Healed tuberculosis.....	16.8	12.6	6.6
102	55	Tuberculosis.....	23.2	7.4	12.2
128	55	Cardiovascular renal condition; sensitized....	14.4
145	55	Glaucoma; Wassermann reaction +.....	18	13.6	16
27	52	Lead poisoning; Wassermann reaction +.....
42	50	Cardiovascular renal condition; myocarditis..	19.2	11.8	9.2
43	50	Normal.....	22	7.4	10
106	50	Tuberculosis.....	18	2.4	14.8
84	50	Cardiovascular renal condition.....	16.4	8.4	10.1
120	50	Purpura.....	21.2	7.2	12.1
29	50	Normal.....	22.8	9.8	7.2
41	50	Normal.....	24	13.2	6.2
79	50	Ulcer.....	19.2	9.4	8.2
101	45	Sensitized.....	19.6	7	10
104	45	Tuberculosis.....	20.8	6.2	12
33	45	Epileptic.....	20	12.6	5.4
100	45	Healed tuberculosis.....	18.8	8.6	12

TABLE 20.—*A Comparison of the Averages Obtained for the Groups Showing Low and High Values of Globulin*

Group	Globulin, %	Reaction to Epinephrine		Reaction to Thyroxin:
		Wheal, Diameter, Mm.	Flare, Radius, Mm.	Wheal, Diameter, Mm.
Group with low level of globulin.....	12	19.2	11.3	16
Group with high level of globulin.....	50	18.7	8.3	10.6

In chart 7, it may be observed that the persons with cardiovascular renal lesions tend to accumulate at the high end of the scale of the globulin, as do the patients with active tuberculosis.

In table 18, we have tabulated the results of some examinations of the twenty persons with the lowest values of globulin and in table 19 of those with the highest values. In the latter group, it is of interest to note that the patient with generalized scleroderma had the highest amount.

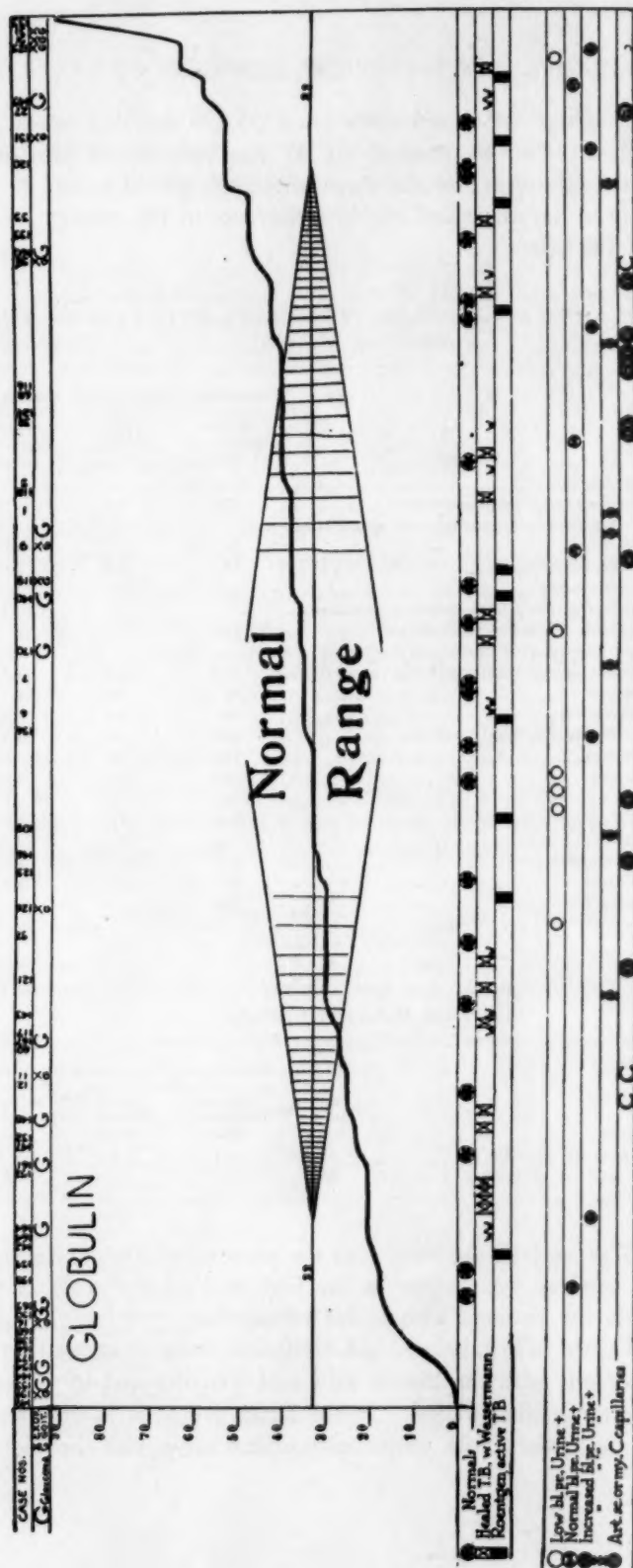


Chart 7.—The amount of globulin in the serum of normal persons and patients with various clinical conditions.

KROMAYER ERYTHEMA TIME

When the skin of the forearm is exposed directly to the light of the Kromayer lamp for thirty seconds, and the time from the beginning of the exposure to the appearance of the erythema determined, a considerable variation in the time, as well as in the intensity of the response, is found.

TABLE 21.—*The Results of Examinations of the Twenty Persons Showing the Most Rapid Reactions to Kromayer Light*

Individual Number	Diagnosis	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Epinephrine, Wheel, Mm.	Thyroxin, Wheel, Mm.	Pigmentation of Skin*	Color of Hair	Kromayer Light Erythema Time, Hr.	CO ₂ Combining Power
45	Cardiovascular renal condition	6	54	0	20	Vagotonic	20.4	16.4	5	Dark brown	3/4	54.3
116	Urticaria.....	3.5	60	17	9	Vagotonic	20.4	5	4	Brown	1/2	55.1
66	Cardiovascular renal condition; arteriosclerosis; myocarditis	6	78	13	1.3	Sympathetico-tonic	20	10.2	3.5	Light brown	5/6	53.1
33	Epilepsy.....	7.5	73	10	-18	Sympathetico-tonic	20	5.4	3	Dark brown	1	54.5
100	Healed tuberculosis..	6	53	9	-1.6	Vagotonic	18.3	12	3	Blond	1	58.3
132	Angioneuritic edema; sensitized	4	73	18	4.8	Vagotonic	26	9	3	Dark brown	1	63.4
156	Hodgkin's disease....	15	61	4	+37	Sympathetico-tonic	19.2	23	...	Dark brown	1	57.3
142	Tumor of the brain..	7	54	7.7	+05	Sympathetico-tonic	18.6	17	5	Dark brown	1	59
168	Orthostatic albuminuria	6	75	12	-0	Vagotonic	18	14	...	Brown	1	55.6
117	Syphilitic arthritis...	6	61	10	-7	Sympathetico-tonic	19.2	20	5	Dark brown	1	52.4
60	Cardiovascular renal condition	8	0	Sympathetico-tonic	19.2	21	4.5	Light brown	1	56.6
149	Nervous.....	10	54	5.4	+5	Vagotonic	20	19	4	Dark brown	1	65.4
7	Cardiovascular renal condition	6	70	11.6	+7	Vagotonic	19.2	15.4	4.5	Light brown	1 11/10	57.9
46	Inanition.....	6	59	10	+13	Sympathetico-tonic	21.2	12.2	1 1/6	56.2
160	Asthma; glaucoma..	15	66	4.4	+16	Vagotonic	16	20	1 1/6	62.7
112	Cardiovascular renal condition	6	54	9	+19.6	Vagotonic	22.4	9.8	4	Dark brown	1 1/6	59
111	Cardiovascular renal condition	6	57	9.5	+31	Sympathetico-tonic	22	10.8	5	Dark brown	1 1/6	55.3
120	Purpura.....	6	82	13	-5	Sympathetico-tonic	21.2	12.1	1 1/5	52.2
49	Syphilis.....	6.75	66	9.7	+8	Sympathetico-tonic	19.2	8	1 1/4	58.3
32	Cardiovascular renal condition	6	60	10	+22	Vagotonic	23.6	9.8	3.5	Brown	1 1/4	54.1

* Indicated on a scale of 1 to 10, 1 being white and 10 "light negro."

Investigators have previously determined that in the white race, the reaction is influenced by, but does not wholly depend on, the degree of pigmentation of the skin. It is known that constitutional factors play a rôle, and in the most practical field, i. e., the treatment of tuberculosis by light, it is common knowledge that a patient who does not react promptly and with production of pigment usually is not benefited by irradiation.

TABLE 22.—*The Results of Examinations of the Twenty Persons with the Slowest Reactions to Kromayer Light*

Individual Number	Diagnosis	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Thyroxin, Wheal, Mm.	Pigmentation of Skin	Color of Hair	Kromayer Light Erythema Time, Hr.	CO ₂ Combining Power
133	Scleroderma.....	2	Sympathetico-tonic	5	Black	Did not appear	50.2
34	Changes in capillaries	7.25	56	7.7	13.6	Vagotonic	18	7.2	3.5	Black	8	56.4
49	Cardiovascular renal condition	6	66	11	7.1	Sympathetico-tonic	12.4	4.2	3.5	Dark brown	5½	59.1
1	Nervous.....	8	68	8.5	7	Sympathetico-tonic	20	13.2	4	Brown	5	62.1
63	Cardiovascular renal condition; arterio-sclerosis	7.5	71	9.4	0.65	Vagotonic	20	12.2	4	Dark brown	5	62.4
99	Healed tuberculosis..	9	73	8.1	-3	Vagotonic	20.4	12.2	3.5	Blond	4½	57.4
107	Myocarditis; arterio-sclerosis; cardiovascular renal condition	9	58	6.4	-65	Vagotonic	20.8	13.4	4	Light brown	4	55.2
127	Cardiovascular renal condition	13	50	3.8	-35	Sympathetico-tonic	18.4	15.4	6	Brown	4	59.1
77	Sensitized.....	9	87	10	+7.9	Vagotonic	14	10	3	Dark brown	4	60.6
79	Ulcer (cardiovascular renal condition)	15	86	5.7	-15.2	Sympathetico-tonic	19.2	8.2	2.5	Black	4	57
128	Cardiovascular renal condition; sensitized	15	58	3.8	-18	Sympathetico-tonic	14.4	6	Dark brown	4	58.1
110	Healed tuberculosis..	7.5	54	7.2	Vagotonic	20.8	12	4	Blond	4	57.2
2	Epilepsy.....	7	69	9.8	-11	Sympathetico-tonic	4	Blond	3½	55.6
78	Normal.....	7	86	12	-0.62	Sympathetico-tonic	19.6	12.4	3.5	Light brown	3½	62.7
18	Healed tuberculosis..	8	70	8.7	+4.2	Vagotonic	3	Brown	3½	58.4
29	Normal (bile pigment in urine)	6.5	70	10.7	3.5	Sympathetico-tonic	22.8	7.2	4.5	Dark brown	3½	60.1
50	Normal.....	8	71	8.8	21	Sympathetico-tonic	24.8	10.4	4	Light brown	3	64.9
85	Fever, unknown origin	6	56	9.3	+18.8	Vagotonic	17.2	14.2	2	Dark brown	3	56.9
75	Cardiovascular renal condition	9	60	6.6	+2.5	Vagotonic	20.4	10	5.5	Dark brown	3	61.6
65	Cardiovascular renal condition	6	61	10	+29	Sympathetico-tonic	15.8	9.2	2.5	Blond	3	53.1

TABLE 23.—*A Comparison of the Averages Obtained for the Groups with Fast and Slow Kromayer Lamp Erythema Times with Those Obtained for the Group of One Hundred "Normal" Men*

Group	Kromayer Light Erythema Time, Hr.	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Epinephrine, Wheal, Mm.	Thyroxin, Wheal, Mm.	Pigmentation of Skin	CO ₂ Combining Power
Group with short erythema time.....	1	7.1	65	10	+7	20	13.8	4	56
Group of 100 "normal" men.....	2	7.5	62	8.2	+8	19.2	11.2	.	57.7
Group with long erythema time.....	3	8.5	66	8.3	+3	19	10.9	4	58.4

In our series of cases, we have roughly estimated the pigment content of the skin in each case by comparing it with a series of filter papers stained with varying dilutions of Bismarck brown. A scale from 1 to 10 was used, 1 being white and 10 approximating the color of the skin of a light negro.

The color of the hair was noted as: blond, black, dark brown, light brown and brown.

During the course of our examination of 100 so-called normal persons, it was shown that the prolongation of the erythema time was associated with a longer blister time, a lowering of the inflammatory index, a low basal metabolic rate, high CO_2 combining power and a lessened wheal due to epinephrine.

When we examine the group of 100 and the clinical material, as well, we find that the shortest time (45 minutes) was noted in patient 45, a man 39 years of age, with a vagotonic reaction to epinephrine and a history of urticaria twenty years previously. His blood pressure is 162 systolic and 114 diastolic (when 4 years of age, he had scarlet fever with involvement of the kidneys). The pigmentation of the skin is 5, and the hair dark brown.

On the other hand, two persons did not react at all. One had scleroderma; the other had an exophthalmic goiter, and had a fairly dark skin (pigment 6) and dark brown hair.

Our truly normal group had a range of erythema time from 75 to 195 minutes.

We have grouped the twenty persons with the shortest erythema times (average 1 hour) in table 21; and we present the twenty with the longest erythema times in table 22. For purposes of comparison, in table 23, we include with the averages for these two groups the averages for the 100 so-called normal men.

It appears that pigmentation, as such, plays comparatively little rôle in the relative rapidity or delay in the appearance of the Kromayer light erythema. Other factors with which the inflammatory index seems associated are probably of more importance. The CO_2 combining power and the endocrine status, particularly a difference in the wheals due to thyroxin are, perhaps, concerned.

Blondness per se is not important. In the group showing delayed reactions, we find four blonds and in the group showing rapidity, none at all.

BASAL METABOLIC RATE

In the introduction, we pointed out that determinations of the basal metabolic rate on a group of nonhospitalized workmen without a possibility of recheck affords a most unsatisfactory examination. We were, however, forced to accept this condition for our group of 100 "normal" men. Our average of +8 is evidence of a lack of absolute rest,

TABLE 24.—The Results of Examinations of the Twenty Persons with the Lowest Basal Metabolic Rates

Individual Number	Basal Metabolic Rate	Diagnosis	Blister Time, Hr.	Permeability Ratio	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Kromayer Light Ery- thema Time, Min.	Skin Resistance	Pulse Rate	Epinephrine, Pulse Pressure, % Increase	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Weight/Length Ratio
37*	-24.4	Normal.....	9	53	10	22.6	2.93	90	0.34	84	-8	Vagotonic	20.4	21.0	10	0	254
13*	-22	Healed tuberculosis.....	8	64	9.6	23.8	2.48	150	0.89	72	+24	Sympathetico- tonic	17.6	6.8	22.6	9.2	223
33	-18	Epilepsy.....	7.5	78	9.5	26.1	2.73	90	1.75	76	+2	Sympathetico- tonic	20	12.6	5.4	0	210
128*	-18	Cardiovascular renal condition.....	15	58	10.2	19.7	1.93	240	1	84	+13	Sympathetico- tonic	14.4	0	180
50*	-18	Tuberculosis.....	6	61	9.8	28.6	2.92	135	0.32	80	+14	Vagotonic	17.2	5.8	13	7.1	247
79*	-15.2	Uter.....	15	83	11.2	20	1.78	240	0.71	76	+8	Sympathetico- tonic	10.2	9.4	8.2	12.2	230
107	-13	Glaucoma.....	15	56	12	22.7	1.9	130	0.55	84	+62	Sympathetico- tonic	17	14.2	15	0	158
118	-11	Tuberculosis (?); arthritis.....	10	87	12.2	17.2	1.4	110	1.9	72	-8	Vagotonic	16.8	7.4	12	8.6	154
17*	-11	Normal.....	8	60	12.7	18.2	1.43	90	0.22	66	0	Vagotonic	20.8	10.2	20.6	10.4	216
108	-9	Epilepsy.....	7	66	12.9	26.1	2.02	210	0.1	100	+64	Sympathetico- tonic
96*	-8	Orthostatic albuminuria.....	6	75	9.40	17.0	1.88	60	0.16	80	+4	Vagotonic	18	16	14	0	215
8*	-8	Nervous.....	9	69	11.4	14.5	1.34	105	0.44	67	+17	Sympathetico- tonic	18.4	11.6	6.2	0	162
122*	-7.3	Normal.....	10	64	10.5	21	2	120	0.48	69	+90	Sympathetico- tonic	20.4	9.8	14	0	197
105	-7	Eosinophilia.....	4	68	10.6	19.2	1.81	...	0.37	68	-3	Vagotonic	20	7.8	12	9	189
117	-7	Syphilitic arthritis.....	7	57	9.1	20.60	2.27	75	0.08	96	-0	Vagotonic	17	11.5	18	0	200
83*	-7	Normal.....	6	61	9.2	17.5	1.8	60	0.25	78	6	Sympathetico- tonic	19.2	6.2	20	0	165
106*	-6.6	Cardiovascular renal condition.....	9	51	8.2	19	2.31	93	0.16	69	+10	Vagotonic	17.2	9.2	13.4	11	258
3*	-6.5	Healed tuberculosis.....	6.5	67	11.1	16.7	1.47	90	0.63	84	-2	Vagotonic	19.6	12.2	6.4	0	243
107*	-6.5	Cardiovascular renal condition.....	9	58	8.1	18.4	2.3	255	0.33	72	-1	Vagotonic	20.8	5.8	13.4	6.2	295
	11.72	Averages and totals.....	8.65	65.8	10.44	20.4	1.98	125	0.565	76.2	+15	11 V., 9.8.	18.9	10.2	12.6	3.8	214

* One of group of 100 "normal" men.

TABLE 25.—The Results of Examinations of the Twenty Persons with the Highest Basal Metabolic Rates

Individual Number	Basal Metabolic Rate	Diagnosis	Bilster Time, Hr.	Permeability Ratio	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Skin Resistance	Pulse Rate	Epinephrine, Pulse Pressure, % Increase	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Weight/Length Ratio	Kromayer Light Erythema Time, Min.
126	+105	Exophthalmic goiter.....	6	..	9.8	18	1.83	0.20	90	+20	Sympathetico-tonic	19.6	7	12	0	174	...
131	+88	Exophthalmic goiter.....	5	77	10.6	18	1.7	0.21	16.8	6.2	10.4	6.2	177	135
31	+73	Exophthalmic goiter.....	5.5	70	9.5	114	21.6	7	7.2	0	240	...
51	+67	Exophthalmic goiter.....	5.5	77	10	25.8	2.58	0.13	104	+25	Sympathetico-tonic	19.2	6.2	9.2	4.8	195	...
125	+59	Exophthalmic goiter.....	6	74	11.51	0.48	140	20.4	7	15.2	16.4	197	90
88*	+54.6	Tuberculosis.....	7.25	54	9.4	13.1	1.4	0.68	76	-10	Vagotonic	18.4	11	12.4	12	203	130
9	+49	Exophthalmic goiter.....	5.5	71	11.5	23.5	2.04	0.75	93	+28	Sympathetico-tonic	200	130
110*	+43.8	Healed tuberculosis.....	7.5	54	12.1	16.3	1.34	0.60	84	-4	Vagotonic	20.8	4.2	12	9.4	190	240
123	+49	Carcinoma of thyroid.....	9.25	74	9.2	20	2.7	...	80	-3	Sympathetico-tonic	20	6.8	10	12.2	263	...
159	+46	Exophthalmic goiter.....	5	69	8.23	17.9	2.17	0.22	76	+17	...	25	9	12	0	181	70
29	+44	Exophthalmic goiter.....	6	73	12.1	18.2	1.5	0.17	92	+31	Sympathetico-tonic	23.4	10	5	1	233	75
58	+43.1	Exophthalmic goiter.....	5	75	12	25.9	2.15	0.10	127	+3	Sympathetico-tonic	19.6	10.4	11.2	0.8	188	66
11	+42	Exophthalmic goiter.....	5	70	10.9	24.1	2.21	0.14	108	+60	Sympathetico-tonic	195	180
150	+39	Glaucoma.....	15	58	12	21.3	1.78	0.22	84	+6	Sympathetico-tonic	17	14	16	0	238	95
158	+37	Hodgkin's disease.....	15	61	9.33	18.58	2	0.29	96	+10	Sympathetico-tonic	19.2	11.3	28	0	173	60
81*	+34.8	Cardiovascular renal condition.....	6	59	8.4	25.8	3.07	0.10	76	+4	Vagotonic	14	6.2	10	0	269	90
47*	+34	Healed tuberculosis.....	5	67	10.4	26.2	2.51	0.13	70	-5	Vagotonic	21.6	5.2	9	0	200	90
119	+34	Adenoma of thyroid.....	6.45	58	9	18.7	2.1	0.08	96	+13	Sympathetico-tonic	24	5	12	7	206	75
170	+33	Glaucoma.....	15	72	10.56	23.71	2.3	0.07	104	170	...
67*	+32	Dwarf.....	6	71	8.8	17.6	2	0.19	75	+8	Vagotonic	17.2	9	13.6	0	195	80
		Averages and totals.....	7.3	67.5	9.81	20.7	2.07	0.23	94.1	+8	10 S., 5 V.	...	7.9	12	4.9	205	108.7

* One of group of 100 "normal" men.

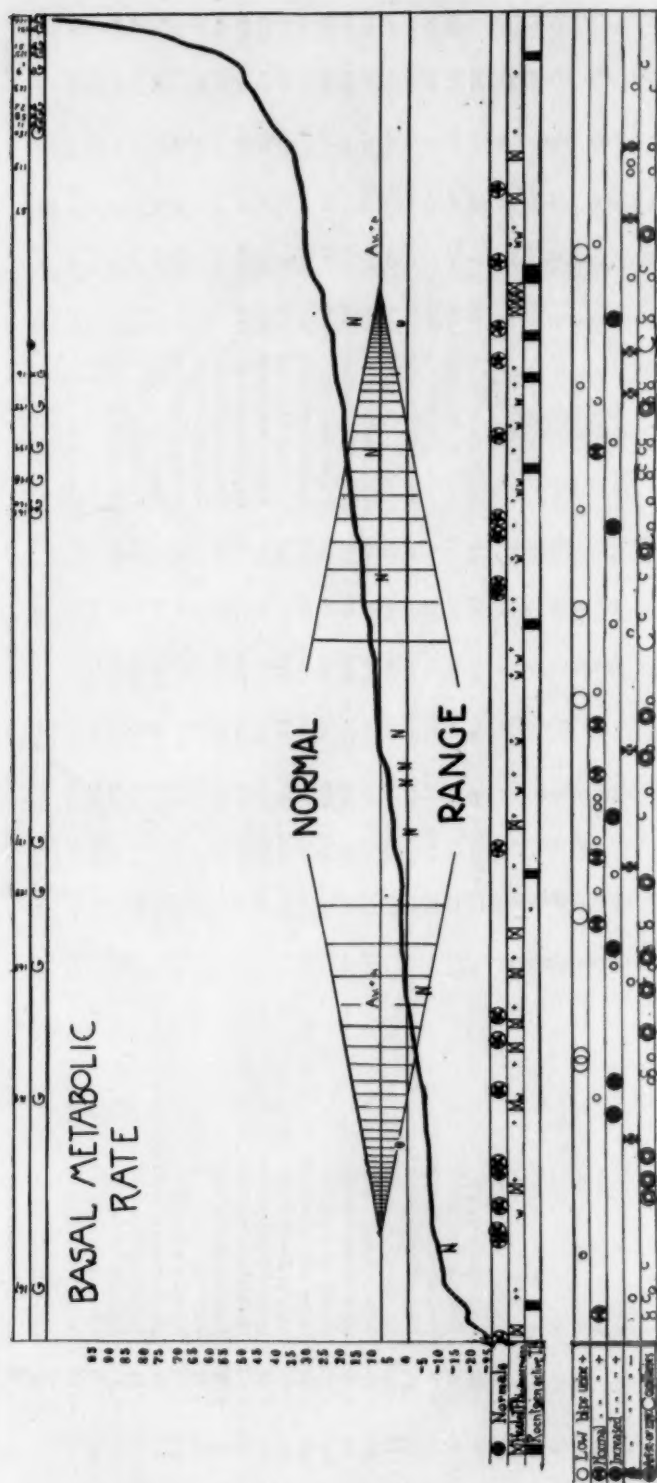


Chart 8.—The basal metabolic rate of normal persons and patients with various clinical conditions.

and the probability exists that, in some cases, food or stimulants had been taken in the morning before the examination.

We have prepared two tables, one including those persons with low basal rates (table 24) and a second including those with extremely high rates (table 25). In this latter table, we have retained the results of the examinations of persons with exophthalmic goiter, contrary to the practice followed in the other tables of results. It will be noted that those with low rates have longer blister times, higher levels of calcium and lower K/Ca ratios, longer Kromayer reaction times and greater skin resistance. They have slower pulse rates and are slightly heavier. The subcutaneous injection of epinephrine hydrochloride shows that, as far as the effect on pulse pressure is concerned, the group with the low ratios has an increase of +15 per cent as compared with +8 per cent of the group with the high ratios, but that there are more sympathicotonic types in the latter group. The intracutaneous injections indicate that the group with the high ratios has smaller flares due to epinephrine and larger flares due to thyroxin.

Examination of chart 8 indicates that the group with roentgenologic evidence of active tuberculosis has higher rates. There is no apparent connection with the cardiovascular renal condition.

RESISTANCE OF THE SKIN TO ELECTRIC CURRENT

The resistance of the skin to electric current varies from a "low" of 0.07 megohms to a "high" of 6.1. The average for the entire group of 100 "normal" men is 0.46.

For the actually normal persons, the range is approximately from 0.15 to 0.45 (average 0.33). Two of our normal group fall outside these limits, patients 29 and 78. These persons have repeatedly been found at the extremes or beyond the normal range, patient 29 being the one in whom a trace of bile was found in the urine.

In table 26, the results of examinations of the ten persons with the lowest skin resistance are tabulated, and in table 27, those of the ten persons with the highest resistance.

Chart 9 shows the curve of the skin resistance. It will be noted that the majority of the persons with roentgenologic evidence of active tuberculosis are on the side of low resistance. There appears to be nothing characteristic about the persons with cardiovascular renal conditions; the persons with glaucoma are scattered over the entire range. On the other hand, the persons with exophthalmic goiter appear to be on the side of low resistance.

TABLE 26.—*The Results of Examinations of the Ten Persons with the Lowest Resistance of the Skin to Electric Current*

Individual Number	Skin Resistance	Diagnosis	Permeability of Capillaries	Basal Metabolic Rate	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
139	0.07	Fröhlch's syndrome.....	73	+ 8	270	Vagotonic	23	9.5	17	6.5
170	0.07	Glaucoma.....	72	+33	170
172	0.08	Syphilis; Raynaud's disease...	72	+18	166	Sympatheticotonic	22.4	16	18	16
166	0.08	Eosinophilia.....	57	- 7	200	Vagotonic	17	11.5	18	0
28	0.08	Healed tuberculosis.....	64	+24.5	200	Sympatheticotonic	20	12.2	7.4	0
104	0.08	Tuberculosis.....	54	+27.5	235	Vagotonic	20.8	6.2	12	0
154	0.09	Glaucoma; arteriosclerosis....	60	+18	181	23	10	26	0
173	0.09	Tumor of the cord.....	57	+12	177	Sympatheticotonic	21	12.5	18	0
105	0.09	Healed tuberculosis.....	62	+31.6	194	Vagotonic	19.6	5.6	12	10.4
135	0.09	Nervous.....	84	+17	183	Vagotonic	12.4	3.2	20	0
	0.07	Averages.....	65.5	18.26	197		26	9.5	16.5	

TABLE 27.—*The Results of Examinations of the Ten Persons with the Highest Resistance of the Skin to Electric Current*

Individual Number	Skin Resistance	Diagnosis	Permeability of Capillaries	Basal Metabolic Rate	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
27	6.1	Lead poisoning; syphilis.....	82	+17	217
112	2.7	Arteriosclerosis; cardiovascular renal condition	54	+19.6	218	Vagotonic	22.4	7.2	9.8	0
73	2.0	Syphilis.....	69	+16.3	191	Vagotonic	17.6	8.2	15.6	0
118	1.9	Tuberculosis; arthritis.....	87	-11	154	Vagotonic	16.8	7.4	12	8.6
137	1.9	Glaucoma.....	61	+ 3.6	16.6	Vagotonic	15.4	10.5	13	0
69	1.9	Nervous; ulcer.....	51	+ 4	160	Sympatheticotonic	21	10	14.4	10.2
33	1.8	Epilepsy.....	73	-18	240	Sympatheticotonic	20	12.6	5.4	0
46	1.7	Inanition.....	59	+13	168	Sympatheticotonic	21.2	13.2	12.2	11.2
80	1.6	Nervous.....	91	+13	212	Vagotonic	14.8	12.4	13.4	9.2
161	1.4	Nervous; glaucoma.....	72	-16	171	Sympatheticotonic	14	13	13	0
	2.3	Averages.....	69.9	7.4	189.7		18	10.5	12	

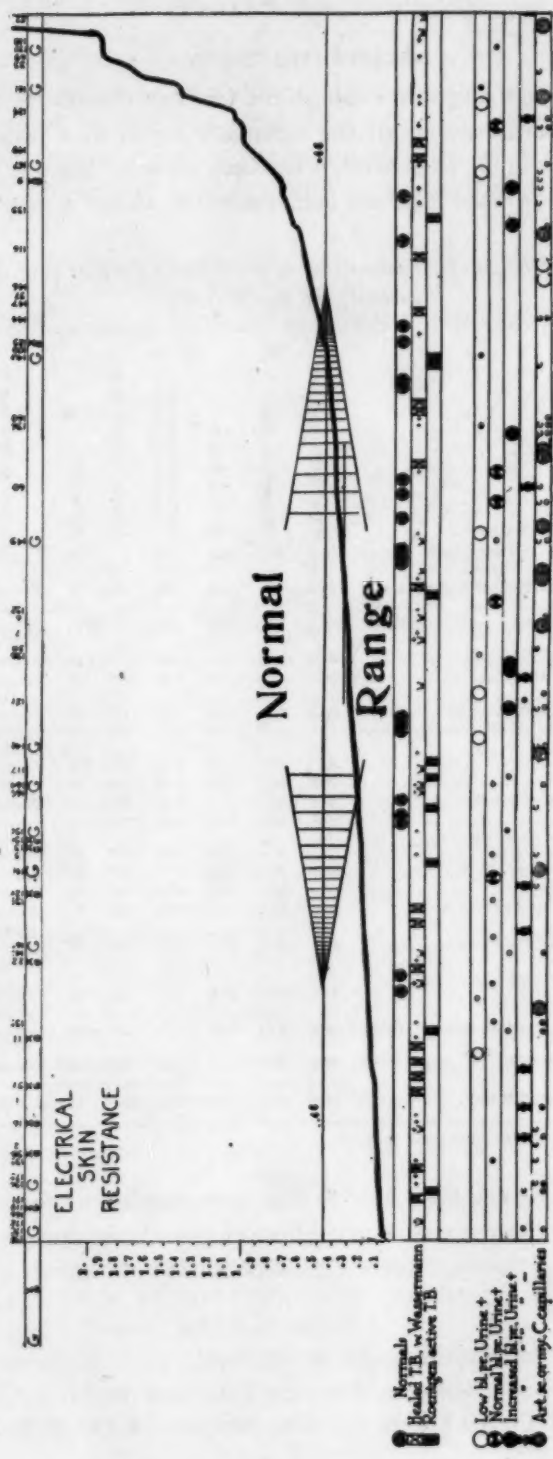


Chart 9.—The resistance of the skin to electric current of normal persons and patients with various clinical conditions.

MUSCLE REACTIVITY

Hopman¹⁰ has sought to establish the fact that the muscle irritability may be used as a criterion of the autonomic status of a person at the time of examination. In general, it has been assumed that the vagotonic person inclines toward alkalosis and, therefore, shows a greater irrita-

TABLE 28.—*The Results of Examinations of the Twenty Persons with the Highest Reactivity of the Muscles*

Individual Number	Muscle Reaction	Diagnosis	CO ₂ Combining Power	Potassium, Mg.	K / Ca Ratio	Skin Resistance to Electric Current	Weight/Length Ratio	Pulse Rate	Vascular Reaction to Epinephrine	Systolic Blood Pressure
140	0.2	Glaucoma; tuberculosis; sensitized	55.6	29.7	2.61	0.45	...	70	Vagotonic	100
132	0.3	Sensitized; healed tuberculosis; eczema	40.3	15	1.12	0.31	234	56	Vagotonic	132
65*	0.4	Cardiovascular renal condition	53.1	16.4	1.67	0.80	221	63	Sympathetico-tonic	100
141	0.4	Glaucoma.....	64.6	23.2	0.20	...	84	Vagotonic	118
108*	0.6	Tuberculosis.....	54.1	15.3	1.47	0.44	196	71	Sympathetico-tonic	94
55*	0.6	Cardiovascular renal condition	56.6	24.9	3.10	0.38	170	84	Vagotonic	128
128*	0.6	Sensitized; cardiovascular renal condition	58.1	19.7	1.93	1	180	84	Sympathetico-tonic	122
139	0.8	Urticaria.....	50	18.4	1.90	0.20	176	104	Vagotonic	113
157	0.8	Glaucoma.....	51.9	18.2	2.24	1.90	166	78	Vagotonic	119
58*	1	Healed tuberculosis.....	52.9	20.9	2	0.13	213	75	Vagotonic	110
78*	1	Normal.....	62.7	18.8	2.23	0.62	203	74	Sympathetico-tonic	122
135	1	Nervous.....	54.5	19.6	1.65	0.09	183	88	Vagotonic	120
77*	1	Sensitized.....	60.6	15.6	1.44	1	187	82	Vagotonic	126
56*	1	Tuberculosis.....	56.6	23.6	2.52	0.32	247	80	Vagotonic	124
117	1	Syphilitic arthritis.....	52.4	17.5	1.80	0.25	195	78	Sympathetico-tonic	130
20*	1	Normal (bile in urine).....	60.1	23.9	2.39	0.74	214	76	Sympathetico-tonic	134
7	1.2	55	0.30	202	68	118
25*	1.2	Tuberculosis.....	59.8	28.8	2.60	0.24	183	86	Sympathetico-tonic	140
14*	1.2	Syphilis; cardiovascular renal condition	55.3	18.3	1.55	0.33	200	92	Sympathetico-tonic	122
104*	1.3	Tuberculosis.....	57.2	22.9	3.00	0.08	235	84	Vagotonic	176
0.82 Averages and totals.....			55.5	21	2.07	4.89	200	78.8	11 V., 8 S.	122

* One of group of 100 "normal" men.

bility. We have not been able to find any such correlation. Goebel and Hillenberg¹¹ were unable to confirm Hopman's conclusions. In the acidosis of pregnancy, Adersberg and Klafter¹² found a distinct increase in irritability.

10. Hopman, R.: *Klin. Wehnschr.* 5:1553, 1926.

11. Goebel, F., and Hillenberg, S.: *Arch. f. Kinderh.* 78:1, 1926.

12. Adersberg, D., and Klafter, E.: *Klin. Wehnschr.* 6:2091, 1927.

When the tables of the results of the examinations of our extreme cases are examined, we find a distinct difference in the types of cases comprising them, as well as marked differences in the blood chemistry. Thus, it will be found that in the group with the greatest irritability are included a number of persons with roentgenologic evidence of active

TABLE 29.—*The Results of Examinations of the Twenty Persons with the Lowest Reactivity of the Muscles*

Individual Number	Muscle Reaction	Diagnosis	CO ₂ Combining Power	Potassium, Mg.	K / Ca Ratio	Skin Resistance to Electric Current	Weight/Length Ratio	Pulse Rate	Vascular Reaction to Epinephrine	Systolic Blood Pressure
94*	10	Normal.....	55.1	17.5	2.06	0.45	236	53	Vagotonic	134
76*	9.6	Cardiovascular renal condition	57.9	20.2	1.87	0.28	230	64	Sympatheticotonic	108
71*	9	Cardiovascular renal condition	57.9	17.5	2	0.36	195	88	Vagotonic	114
39*	8.5	Syphilis.....	55.7	18	1.91	0.29	254	82	Vagotonic	138
79*	7.7	Ulcer; cardiovascular renal condition	57	20	1.78	0.71	220	76	Sympatheticotonic	140
61*	7.4	Cardiovascular renal condition	53.1	17.9	2.35	0.28	208	64	Vagotonic	142
45*	7.4	Cardiovascular renal condition	54.3	16.6	1.48	0.28	317	84	Vagotonic	162
32*	7.4	Cardiovascular renal condition	54.1	26.1	2.73	0.18	190	74	Vagotonic	144
53*	6.7	Normal.....	53.9	22.8	...	0.35	231	80	Vagotonic	125
15*	6	Healed tuberculosis.....	57.6	18.8	1.55	0.19	210	60	Sympatheticotonic	128
17*	6	Normal.....	59.1	18.2	1.43	0.22	216	65	Vagotonic	130
82*	5.7	Cardiovascular renal condition	58.8	17.2	1.50	0.20	206	62	Sympatheticotonic	170
98*	5.5	Cardiovascular renal condition	62.7	17	1.98	0.20	212	64	Vagotonic	136
75*	5.4	Cardiovascular renal condition	61.6	19.2	1.78	0.13	243	77	Vagotonic	146
47*	5	Healed tuberculosis.....	56.4	26.2	2.51	0.13	260	70	Vagotonic	136
20*	5	Tuberculosis.....	62.7	17.4	1.53	0.25	225	80	Vagotonic	130
62*	5	Cardiovascular renal condition	56.8	15.2	1.30	0.15	221	64	Vagotonic	140
64*	5	Normal; nervous.....	55	16.6	1.84	0.22	208	64	Vagotonic	112
68*	4.4	Healed tuberculosis.....	51.1	17.1	1.94	0.53	217	89	Sympatheticotonic	131
63*	5	Cardiovascular renal condition	62.4	20.9	1.83	0.65	190	60	Vagotonic	116
6.58 Averages and totals.....			57.1	19.1	1.85	0.30	224	71	15 V., 5 S,	134

* One of group of 100 "normal" men.

tuberculosis, as well as sensitized persons. In the group with the lower irritability are many persons with cardiovascular renal lesions and increased blood pressure (tables 28 and 29).

The persons with the greatest irritability have more serum potassium, higher K/Ca ratios, greater skin resistance and higher pulse rates and are somewhat lighter in weight.

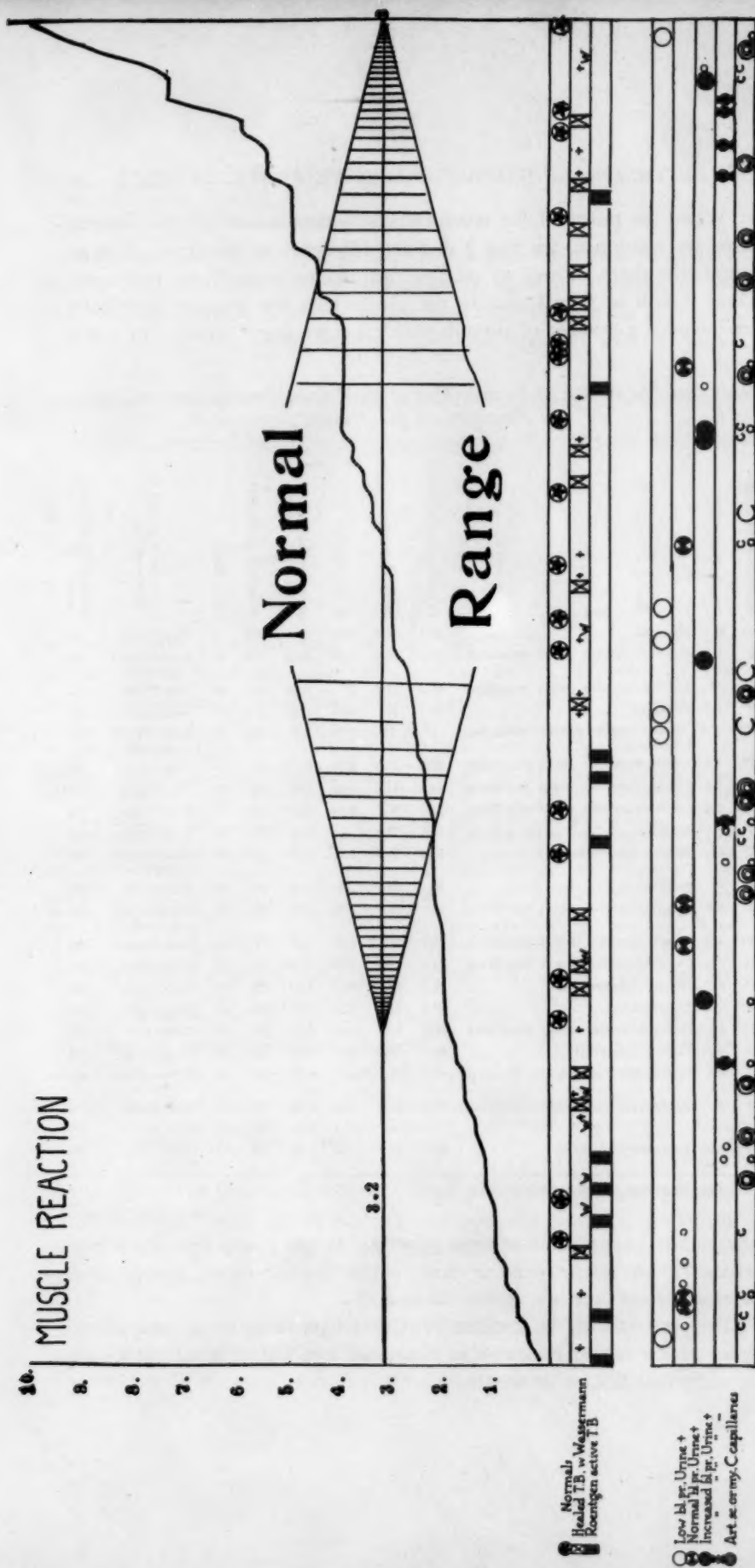


Chart 10.—The muscle reactivity of normal persons and patients with various clinical conditions.

REACTION OF PULSE PRESSURE TO EPINEPHRINE

In a previously published paper,⁸ we made an analysis of the present material when the results of the reaction to epinephrine (subcutaneous injection of 0.5 cc. of epinephrine hydrochloride, 1 to 1,000) are estimated wholly on the increase or decrease in the systolic blood pressure. In that paper, we pointed out that when we selected a group of ten of the most markedly sympathetotonic persons and compared them with the ten most markedly vagotonic persons, the sympathetotonic ones had higher calcium levels, but lower K/Ca ratios, shorter Kromayer lamp erythema times, lower blood pressures and CO₂ combining powers, lower weight/length ratios and somewhat greater wheals due to thyroxin, and greater flares due to epinephrine and thyroxin.

When we examine tables 30 and 31 containing the results of the examinations of the twenty persons showing the greatest and the least reactivity to epinephrine based on the percentage of increase or decrease in pulse pressure for one hour following the injection, we, of course, deal with a somewhat different group of persons. In both instances, we deal with persons who give either a primary sympathetotonic or a vagotonic systolic reaction, but inclusion in this group will depend rather on the sustained character of these reactions.

The blister times for the sympathetotonic group so constituted are longer, the levels of calcium are somewhat higher, the blood pressures are lower, the levels of the blood sugar are higher and the persons are not so heavy. The flares due to epinephrine and the wheals due to thyroxin are larger.

In our former study of this material, we found that the low K/Ca ratio which Kylin assumed for the sympathetotonic group was apparent only for a relatively small, selected group, while many of the persons with a distinctly sympathetotonic type of reaction had high ratios. It should be noted that with the present classification, the difference in the ratio which Kylin postulates does not appear. In general, however, the sympathetotonic group has a higher level of calcium.

Chart 11 reveals the wide range of our normal persons, as well as of the persons with cardiovascular renal conditions. In the latter group, however, certain differences do appear. Those with low blood pressures and positive evidence of changes in the urine appear at the vagotonic end. Patients with exophthalmic goiter, as might be anticipated, are found toward the sympathetotonic end.

TABLE 30.—The Results of Examinations of the Twenty Persons with the Greatest Increases of Pulse Pressure Following the Subcutaneous Injection of Epinephrine Hydrochloride

Individual Number	Reaction to Epinephrine: Pulse Pressure Increase, %	Diagnosis	Bilateral Time, Hr.	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Globulin, Mg.	Blood Pressure, Systolic	Blood Pressure, Diastolic	Sugar, Mg.	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
8*	90	Normal.....	10	64	6.4	10.5	21	3	45	120	86	73	107	Sympatheticotonic +	20.4	9.8	14.2	0
54*	66	Cirrhosis; cardiovascular renal condition.....	6	60	10	22	33	103	68	80	256	Sympatheticotonic -	21.2	13.4	12	0
9*	64	Epilepsy.....	7	69	9.8	12.9	26.1	2	..	100	68	74	...	Sympatheticotonic +
167	63	Glaucoma.....	15	56	8.7	12	22.7	1.9	27	137	92	81	158	Sympatheticotonic +	17	14.2	15	0
127*	60	Cardiovascular renal condition.....	13	50	3.8	12.2	16.2	1.33	33	106	76	81	180	Sympatheticotonic +	18.4	9.7	15.4	12
172	57	Raynaud's disease.....	12	72	6	13	21.3	1.64	..	108	78	76	166	Sympatheticotonic +	22.4	16	19	16
24*	50	Healed tuberculosis.....	6	70	11.5	11.7	24.8	2.12	60	116	58	81	219	Sympatheticotonic +	16.8	12.6	6.6	0
144	50	Cardiovascular renal condition; pellagra	15	35	2.2	9.8	17.9	1.79	2	100	80	90	174	Sympatheticotonic +	14.4	11.5	15	0
92*	46	Nervous.....	9	82	9	8.4	19.5	2.32	26	110	60	67	210	Sympatheticotonic +	20.4	10.2	15.2	7.6
145	43	Glaucoma.....	15	67	4.4	10.1	15.7	1.55	55	136	80	70	166	Sympatheticotonic -	18	13.0	16	0
87*	40	Normal.....	6	56	9.3	8.4	19.5	2.32	30	104	62	94	200	Sympatheticotonic +	16	8.8	12	5.4
69*	37	Cardiovascular renal condition.....	6	78	13	11	20	1.8	..	128	66	67	257	Sympatheticotonic +	20	9.2	10.2	0
133	36	Scleroderma.....	13.2	17.5	1.32	90	92	68	77	...	Sympatheticotonic +
1	35	Neurosis.....	8	68	8.5	12.1	24.9	2	38	132	74	113	202	Sympatheticotonic +	20	8	13.2	9.6
25*	35	Tuberculosis.....	6	57	9.4	11.1	28.8	2.6	19	140	80	67	183	Sympatheticotonic +	21.2	12.2	9	15.2
142	33	Tumor of the brain.....	7	54	7.7	9.4	18.3	1.95	19	108	78	97	200	Sympatheticotonic +	18.6	8.7	17	0
35*	33	Normal.....	8	54	6.7	8.7	25.2	2.9	33	108	78	79	203	Sympatheticotonic -	22.8	11	9.2	0
53*	32	Normal.....	8	62	7.7	22.8	25	125	73	77	211	Sympatheticotonic -	17.2	11.8	12.2	11.2
68*	31	Healed tuberculosis.....	7	78	11	8.8	17.1	1.94	30	131	76	68	217	Sympatheticotonic -	19.3	9.6	12	7
82*	31	Cardiovascular renal condition.....	6	53	9.6	11.4	17.2	1.5	33	170	98	58	208	Sympatheticotonic +	21.2	7	13	0
20	41	Averages.....	8.9	62	7.8	10.8	20.9	1.93	35	113	73	73	165		20	10.8	13	4.6

* One of group of 100 "normal" men.

TABLE 31.—The Results of Examinations of the Twenty Persons with the Lowest Increases of Pulse Pressure Following the Subcutaneous Injection of Epinephrine Hydrochloride

Individual Number	Reaction to Epinephrine: Pulse Pressure Increase, %	Diagnosis	Bilester Time, Hr.	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Globulin, Mg.	Blood Pressure, Systolic	Blood Pressure, Diastolic	Sugar, Mg.	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
116	—17	Urticaria.....	3.5	60	17	10	19.4	1.94	40	128	50	78	195	Vagotonic	20.4	7.4	5	0
121	—13	Arthritis deformans.....	6	60	11.5	8.9	20.2	2.27	30	148	80	74	224	Vagotonic	26	5.6	8	0
88*	—12	Nervous.....	15	58	3.8	12.6	13.9	1.23	40	118	60	94	176	Vagotonic	18.8	14	15.4	12.4
129*	—10	Tuberculosis.....	15	52	2.5	11.5	19	1.65	42	116	68	83	219	Vagotonic	18.4	7	12.2	0
88*	—10	Tuberculosis.....	7.25	53	8.1	9.4	13.1	1.4	33	128	76	79	233	Vagotonic	18.4	11	12.4	12
135	—10	Nervous.....	6	84	14	11.9	19.6	1.65	45	130	60	75	183	Vagotonic	12.4	3.2	20	0
75*	—9	Cardiovascular renal condition....	9	60	6.6	10.8	19.2	1.78	38	146	80	75	243	Vagotonic	20.4	10.8	10	0
118	—8	Arthritis.....	10	57	8.7	12.2	17.3	1.4	38	120	60	80	154	Vagotonic	16.8	7.4	12	8.6
67*	—8	Dwarf.....	6	71	11.8	8.8	17.6	2	33	125	80	86	195	Vagotonic	17.2	9	13.6	0
37*	—8	Normal.....	9	56	6.2	10	22.6	2.26	42	116	70	75	254	Vagotonic	20.4	21.6	10	0
70*	—8	Arthritis.....	10.5	74	7	11.4	16.6	1.45	34	148	50	67	214	Vagotonic	18	11	10	0
47*	—5	Healed tuberculosis.....	5	62	12.8	10.4	26.2	2.51	40	136	64	72	266	Vagotonic	21.6	5	9	0
132	—5	Angioneurotic edema.....	4	73	18	9.8	20.1	2.05	29	130	74	63	243	Vagotonic	23	7.5	9	8
108*	—5	Cardiovascular renal condition....	6	71	12	11.2	19	1.60	37	150	80	65	243	Vagotonic	19.6	7	11.2	0
110*	—4	Healed tuberculosis.....	7.5	54	7.2	12.1	16.3	1.34	28	110	62	61	190	Vagotonic	20.8	4.2	12	9.4
123	—3	thyroidism Carcinoma of thyroid; hyper- thyroidism	9.25	74	8	9.2	20	2.17	32	165	110	81	263	Vagotonic	20	6.8	10	12.2
45*	—3	Cardiovascular renal condition....	6	54	9	11.2	16.6	1.48	40	102	114	77	317	Vagotonic	20.4	9.8	16.4	12
122*	—3	Normal.....	4	68	17	10.6	19.2	1.81	35	102	56	56	189	Vagotonic	—	7.8	12	9
103*	—1	Cardiovascular renal condition....	6	52	8.6	9.2	17.3	1.88	40	126	70	57	270	Vagotonic	22.4	9	12.2	0
107*	—1	Cardiovascular renal condition....	9	58	6.4	8	18.4	2.3	40	134	72	60	265	Vagotonic	20.8	5.8	13.4	6.2
—7	Averaged.....		7.7	64	9.6	10.4	18.6	1.8	44	128	71	71	232		19.8	8.3	11.6	4.4

* One of group of 100 "normal" men.

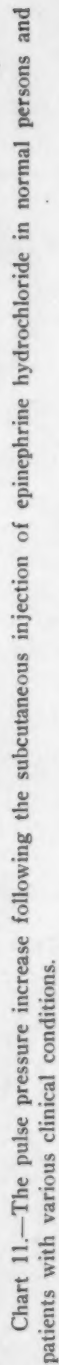


Chart 11.—The pulse pressure increase following the subcutaneous injection of epinephrine hydrochloride in normal persons and patients with various clinical conditions.

CO₂ COMBINING POWER

The average CO₂ combining power of the serum of the 100 "normal" men was 57.7. The range for the strictly normal persons was from 52 to 65. Chart 12 indicates that all the persons in the healed tuberculous group are uniformly distributed over the normal range; the per-

TABLE 32.—*The Results of Examinations of the Ten Persons with the Lowest CO₂ Combining Powers*

Individual Number	CO ₂ Combining Power	Diagnosis	Potassium, Mg.	Calcium, Mg.	Ice Reaction Time, Seconds	Weight/Length Ratio	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
132	40.3	Eczema.....	15	13.4	10	234	18.4	9.4	13.4	5
167	47.9	Glaucoma.....	22.7	12	5	158	17	14.2	15	0
171	48.7	Urticaria.....	17.9	12.6	20	161	17.5	10.5	18	0
161	49.4	Glaucoma.....	18	9.2	12	171	14	13	13	0
106	49.5	Cardiovascular renal condition	19	11.2	30	243	19.6	7	11.2	0
139	50	Urticaria.....	18.4	9.7	8	176	16	11	14	12.5
68	51	Healed tuberculosis.....	17.1	8.8	10	217	19.2	9.6	12	7
109	51.4	Neurosis.....	16.1	10.8	25	140	18	9	12	9.4
115	51.8	Cardiovascular renal condition	15.2	7.8	10	215	17.2	6	14.2	8
137	51.9	Glaucoma.....	18.2	8.1	30	166	15.4	10.5	13	0
	49.2	Averages.....	17.7	10.36	16	188	17.2	10	13.5	4.19

TABLE 33.—*The Results of Examinations of the Ten Persons with the Highest CO₂ Combining Powers*

Individual Number	CO ₂ Combining Power	Diagnosis	Potassium, Mg.	Calcium, Mg.	Ice Reaction Time, Seconds	Weight/Length Ratio	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
153	73.2	Glaucoma.....	18.7	9	30	223	22	6.5	18	0
150	72.7	Glaucoma.....	21.3	12	7	238	17	14	16	0
146	71	Myasthenia.....	14.4	9.2	30	192	18	12	19	0
145	69.5	Glaucoma.....	24.3	9.7	10	182	18	12	17	0
28	66	Healed tuberculosis.....	24.1	11	25	200	20	12.2	7.4	0
149	65.4	Nervous.....	17	10.1	15	209	20	9.7	19	0
14	65	Cardiovascular renal condition	19.6	11.2	40	198	24.4	6.2	15	5
50	65	Normal.....	27.4	18.4	15	237	24.8	10.6	10.4	10
4	64.3	Normal.....	21.2	11.8	40	237	22.8	10.6	10.2	0
105	64.4	Healed tuberculosis.....	17.1	9	15	194	19.6	5.6	12	10.4
	67.6	Averages.....	20.5	10.4	22.7	211	20.6	9.94	14.4	2.5

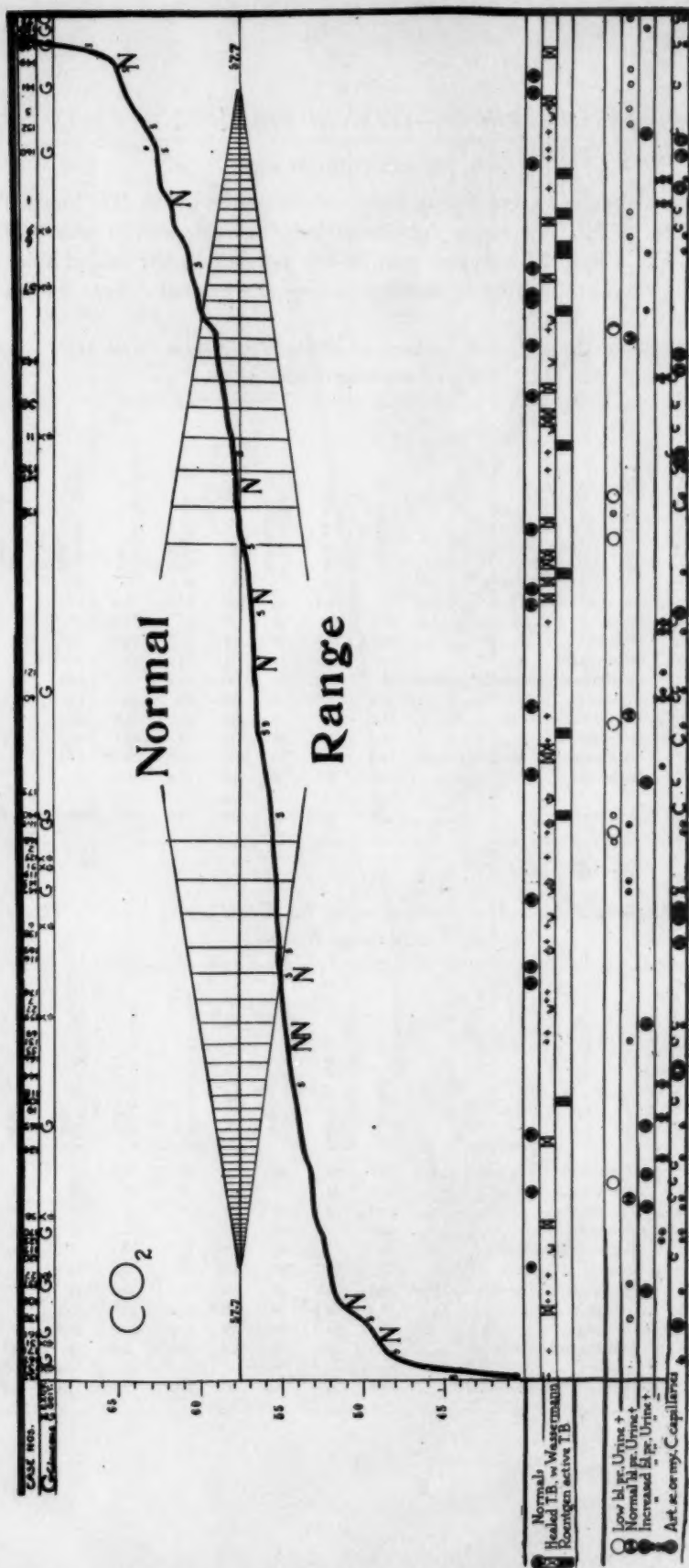


Chart 12.—The CO_2 combining power of the serum of normal persons and patients with various clinical conditions.

sons with active tuberculosis tend to appear at the upper end of the curve. There appears to be nothing characteristic in the distribution of the various groups with cardiovascular renal conditions, unless it is the fact that those with increased blood pressure and urinary changes appear at the low end of the scale.

Sensitized and nervous persons are found over the entire range. More of the patients with exophthalmic goiter and glaucoma are found on the side below the average.

We have tabulated the results of some examinations of the ten persons with the lowest and of the ten with the highest CO_2 combining powers in tables 32 and 33.

It will be observed that the person (no. 132) with the lowest CO_2 combining power is the one with eczema who previously was outstanding because of a low K/Ca ratio. Two persons with urticaria also appear in this group. The types of persons in the group with high CO_2 combining power are of no particular interest. The chief divergencies of the group with low CO_2 combining power appear to be their shorter ice reaction times and smaller wheals due to epinephrine. The potassium values, too, are perceptibly diminished.

ICE REACTION TIME

The rapidity with which an erythema appears following the local application of ice to the skin affords some insight concerning the activity of the peripheral vasomotor apparatus. In these observations, we have uniformly used the chest wall. In the table of correlation (part I, table 1), we have shown the following apparent correlations of the ice reaction time: delay of the reaction (1) with increasing level of calcium; (2) with increasing metabolic rate; (3) with increasing CO_2 combining power (except with exophthalmic goiter); (4) with increasing age; (5) with decrease of the flare due to thyroxin and of the wheal to caffeine; and acceleration with increasing weight/length ratio.

Tables 34 and 35, based, respectively, on the extremely rapid reaction and the delayed reaction, confirm the relation to the level of calcium, to the metabolic rate, to the weight/length ratio, to age and to the flare due to thyroxin. In addition, it appears that with delayed ice reaction, the resistance of the skin to electric current is greater. The proportion of sympathetotonic persons is slightly larger in the group with short ice reaction time.

When we examine chart 13, we find the strictly normal group scattered over the entire curve, but it may be observed that almost half of the group are clustered in one region (the range from 18 to

TABLE 34.—*The Results of Examinations of the Twenty Persons with the Most Rapid Reactions to Local Application of Ice to the Chest*

Individual Number	Ice Reaction Time, Seconds	Diagnosis	Calcium, Mg.	Inflammatory Index	Protein, Mg.	Skin Resistance to Electric Current	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Thyroxin, Flare, Mm.	Caffein, Wheal, Mm.	Weight/Length Ratio	Age
67*	4	Dwarf.....	8.8	11.8	6.98	0.10	32	Vagotonic	0	33.4	195	47
122*	5	Normal.....	10.6	17	8.06	0.37	-7.3	Vagotonic	0	21.2	189	33
100*	5	Healed tuberculosis.....	0	9	7.85	0.11	-1.6	Vagotonic	29.2	27	241	45
165	5	Glaucoma.....	10	5.4	8.28	0.18	0.5	0	15	250	52
168	5	Orthostatic albuminuria..	9.4	12	7.41	0.16	-0	Vagotonic	0	22	215	28
167	5	Glaucoma.....	12	3.7	8.71	0.85	-13	Sympathetico- tonic	0	158	77
142	5	Tumor of the brain.....	9.4	7.7	7.69	0.17	+5	Sympathetico- tonic	0	30	200	53
106*	5	Cardiovascular renal condition	9.2	8.6	7.73	0.39	+2	Vagotonic	0	18.2	270	50
61*	7	Cardiovascular renal condition	7.6	11.6	7.41	0.23	+1	Vagotonic	0	20.2	208	51
41*	7	Normal.....	9.8	9.1	8.49	0.26	+15	Vagotonic	0	5.8	216	40
64*	7	Healed tuberculosis.....	10.1	13	8.70	0.42	-12.4	Vagotonic	7.2	12.2	230	40
64*	7	Normal.....	9	10	7.41	0.22	+23	Sympathetico- tonic	11.6	16.2	208	31
43*	7	Normal.....	9.2	9.7	7.63	0.27	-4.4	Sympathetico- tonic	0	11	231	45
150	7	Glaucoma.....	12	3.8	7.85	0.22	+39	Vagotonic	0	22	238	67
139	8	Urticaria.....	9.7	11	7.10	0.20	+5	Vagotonic	12.5	14	176	29
78*	10	Normal.....	8.4	12	8.49	0.62	-6.2	Sympathetico- tonic	6.2	20	203	33
18*	10	Healed tuberculosis.....	14.5	8.7	8.30	1	+4.2	Vagotonic	200	31
95*	10	Healed tuberculosis.....	7.8	9.8	8.5	0.39	+20	Sympathetico- tonic	6.2	26.2	220	54
59*	10	Normal.....	9.6	8.6	7.85	0.16	-0.5	Vagotonic	8	23.4	252	37
68*	10	Healed tuberculosis.....	8.8	11	8.66	0.53	+25.8	Sympathetico- tonic	7	22.4	217	35
6.9	Averages and totals....		9.74	9.67	7.96	0.349	+5.9	7 S., 12 V.	5.1	20	215	44.3

* One of group of 100 "normal" men.

TABLE 35.—*The Results of Examinations of the Twenty Persons with the Least Rapid Reactions to the Application of Ice to the Chest*

Individual Number	Ice Reaction Time, Seconds	Diagnosis	Calcium, Mg.	Inflammatory Index	Protein, Mg.	Skin Resistance to Electric Current	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Thyroxin, Flare, Mm.	Caffein, Wheal, Mm.	Weight/Length Ratio	Age
91*	45	Cardiovascular renal condition	8	7.85	0.30	-1.7	Vagotonic	9.4	22.2	208	66
76*	45	Arthritis; cardiovascular renal condition	11.4	7	8.65	0.39	+23	Vagotonic	0	24.6	264	65
81*	45	Pruritis; cardiovascular renal condition	8.4	10	8.49	0.10	+34.8	Vagotonic	0	16.4	209	69
136	45	Arteriosclerosis; pellagra	10	5	9.28	0.39	+20	Sympathetico- tonic	0	16	180	44
172	45	Raynaud's disease.....	13	6	8.16	0.08	+18	Sympathetico- tonic	16	20	166	30
14*	40	Cardiovascular renal condition	11.2	10.5	8.06	0.20	+2.7	Vagotonic	5	9.8	198	36
40*	40	Changes in capillaries.....	10.8	6.6	8.70	0.39	+22	Vagotonic	0	5.8	201	40
40*	40	Changes in capillaries.....	10.2	6.6	8.70	0.39	+22	Vagotonic	0	5.8	201	40
96*	40	Cardiovascular renal condition	8.2	7	7.23	0.11	+31	Vagotonic	0	28.4	213	70
102*	40	Tuberculosis.....	10.6	5.8	7.95	0.20	+22	Vagotonic	0	18.2	170	65
140	40	Tuberculosis; glaucoma..	11.4	4.06	6.77	0.45	Vagotonic	0	30	45
15*	38	Healed tuberculosis.....	12.1	7.5	7.95	0.19	-4.5	Sympathetico- tonic	12	12.4	210	60
26*	35	Syphilis.....	10.2	11	8.28	0.28	+9.6	Vagotonic	6.4	11.6	210	30
48*	35	Syphilis.....	9.6	9.7	8.50	0.10	8.3	Sympathetico- tonic	0	7	222	46
77*	35	Sensitized.....	10.8	10	6.98	1	7.9	Vagotonic	15.4	17	187	39
73*	35	Syphilis.....	11.2	7.6	8.5	2	16.3	Vagotonic	0	20	191	48
158	35	Hodgkin's disease.....	9.3	4	8.28	0.29	37	Sympathetico- tonic	0	22	173	49
42*	32	Cardiovascular renal condition	11.4	6.5	7.63	0.15	6.8	Vagotonic	4.6	5.8	211	33
80*	30	Nervous.....	8	15.1	8.28	1.6	13	Vagotonic	9.2	16.2	212	30
106*	30	Cardiovascular renal condition	11.2	12	8.06	0.63	-6.6	Vagotonic	0	25.6	243	60
137	30	Glaucoma.....	8.1	4	8.49	1.9	3.6	Vagotonic	0	18	166	61
38	Averages and totals....		10.3	7.86	8.11	0.537	+12	15 V., 5 S.	3.9	19.96	204	49.3

* One of group of 100 "normal" men.

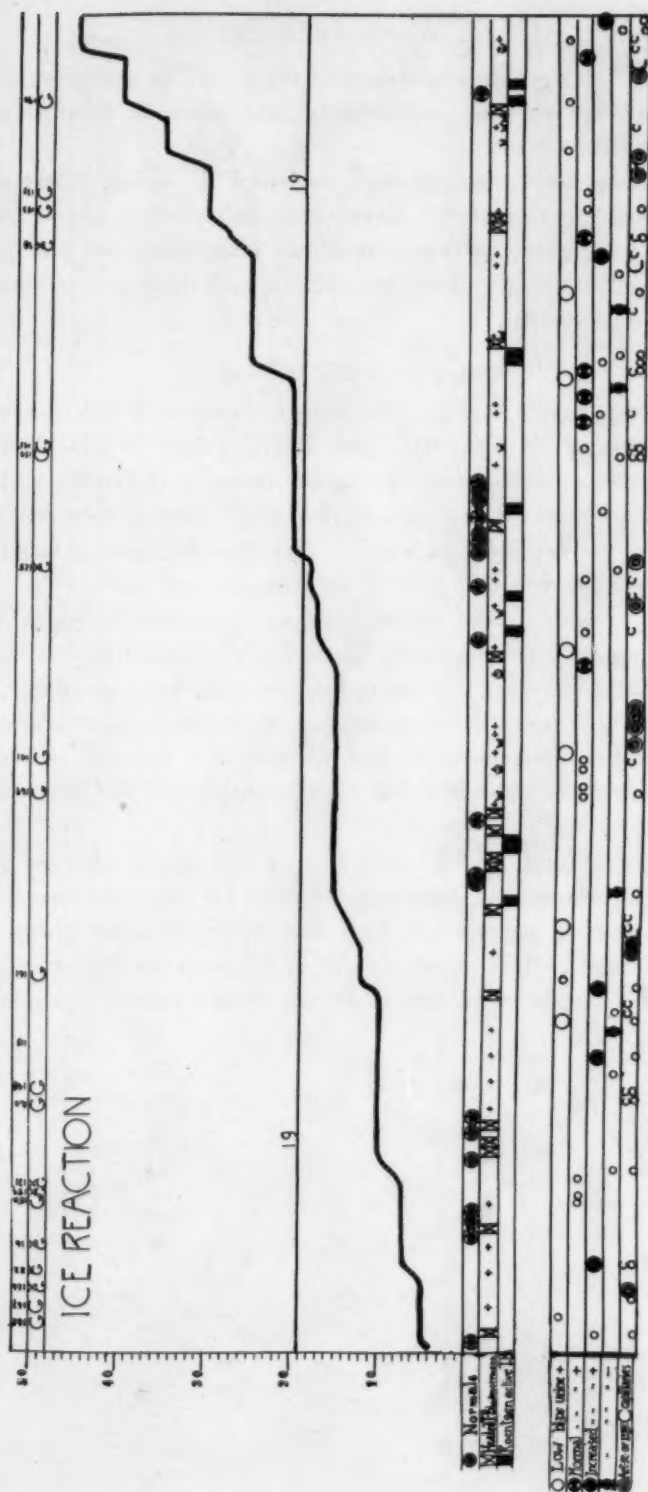


Chart 13.—The ice reaction time of normal persons and patients with various clinical conditions.

20 minutes). This group is composed of those persons who were noted for relatively low capillary permeability, and some of them show a sluggish capillary circulation.

The persons with roentgenologic evidence of active tuberculosis appear toward the side of the curve representing delay, and it seems that more of the group with cardiovascular renal conditions are found here. The advanced ages of the members of both these groups must be taken into consideration.

WEIGHT/LENGTH RATIOS

The average weight/length ratio (weight in pounds, length in inches) for our group of 100 "normal" men is 217 (chart 14). When we select the twenty persons with the highest ratios, it is evident that the group includes most of the persons in whose cases a roentgenologic diagnosis of myocarditis was made. The majority give a vagotonic reaction to epinephrine, and their K/Ca ratios average 2.06.

In part I, table 1, the correlations with the weight/length ratio indicate that as the ratio increases the capillary permeability diminishes, the K/Ca ratio increases, the sugar increases, the basal metabolic rate decreases, as also does the skin resistance, the pulse pressure on subcutaneous injection of epinephrine hydrochloride and the CO₂ combining power increase, and the wheal due to epinephrine and the flare due to morphine increase.

In tables 36 and 37, the averages for the sugar and the basal metabolic rate show little difference between the two extreme groups, but there are more persons with high skin resistance in the group with the highest ratios. The wheals due to epinephrine are larger here, as are the flares due to morphine, while the wheals due to thyroxin are smaller.

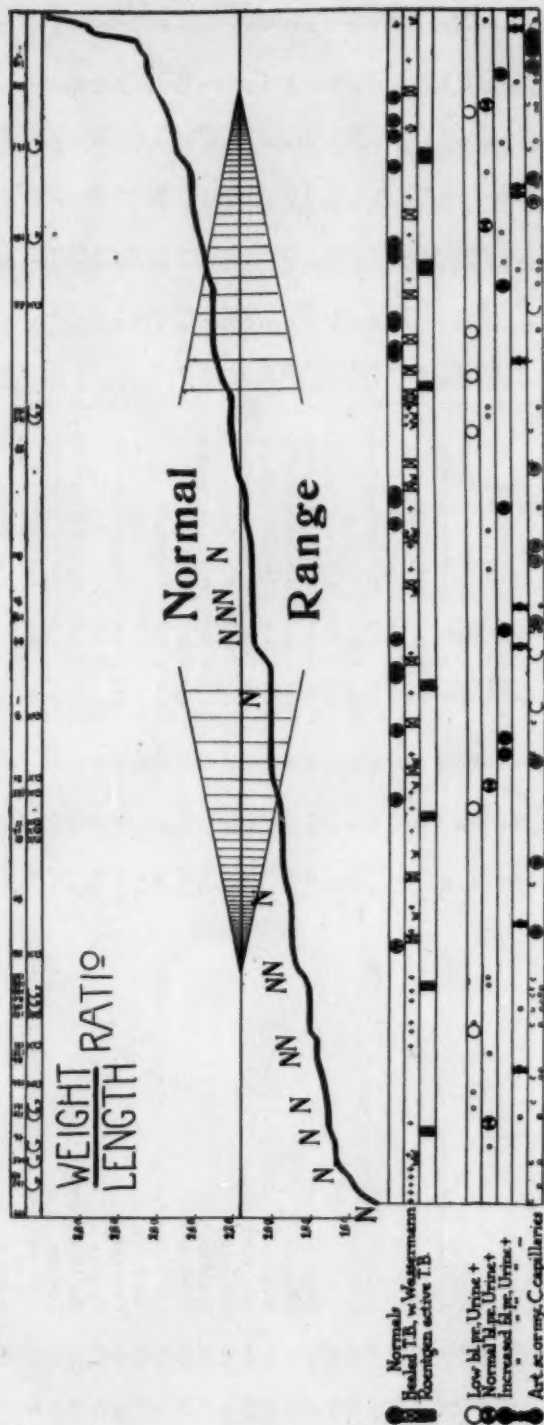


Chart 14.—The weight length ratio of normal persons and of patients with various clinical conditions.

TABLE 36.—The Results of Examinations of the Twenty Persons with the Lowest Weight/Length Ratios

Individual Number	Weight/Length Ratio	Diagnosis	K / Ca Ratio	Sugar, Mg.	Basal Metabolic Rate	Skin Resistance to Electric Current	CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Morphine, Wheal, Mm.	Morphine, Flare, Mm.	Thyroxine, Wheal, Mm.	Thyroxine, Flare, Mm.
174	143	Raynaud's disease.....	2	90	4	55	Vagotonic	0
169	140	Neurosis.....	1.5	67	0.47	51.4	Vagotonic	3	18	9	9	7.2	12	9.4
147	142	Postencephalitis.....	2	79	-6	0.54	57.9	Sympathetico tonic	8	18	11.6	12	7.4	13	0
118	154	Arthritis.....	1.4	80	-11	1.9	54.2	Vagotonic	-8	10.8	7.4	10	6.8	12	8.6
167	138	Glaucoma.....	1.9	81	-13	0.85	47.9	Sympathetico tonic	+62	17	14.2	12	9	15	0
69	160	Ulcer; nervous.....	1.66	70	+4	1.9	54.8	Sympathetico tonic	0	21.2	10	12.2	22	14.4	10.2
171	161	Urticaria.....	1.42	72	8	0.68	48.7	Sympathetico tonic	12	17.5	10.5	12.5	0	18	0
145	166	Wassermann reaction +; glaucoma.....	1.55	70	19	0.35	55.4	Sympathetico tonic	43	18	13.6	16	0	16	0
172	163	Raynaud's disease.....	1.64	76	18	0.68	Sympathetico tonic	57	22.4	16	15.5	8.5	18	16
137	163	Glaucoma.....	2.21	73	3.6	1.9	51.9	Vagotonic	7	15.4	10.5	12.5	10	13	0
46*	168	Inanition.....	1.24	61	13	1.7	56.2	Sympathetico tonic	15	21.2	13.2	15	16.2	12.2	11
102*	170	Tuberculosis.....	1.63	62	22	0.90	60.9	Vagotonic	11	23.2	7.4	10.8	15	12.2	0
55*	170	Cardiovascular renal condition (urine).....	3.1	73	6.2	0.33	56.6	Vagotonic	5	17.6	8.2	10.2	19.6	11.2	0
170	170	Glaucoma.....	2.2	330	33	0.07	52.5
161	171	Glaucoma.....	1.96	86	16	1.4	49.4	Sympathetico tonic	25	14	13	5.5	10.7	13	0
130	172	Purpura.....	1.90	71	-5	52.2	21.2	7.2	9.6	8.2	12	0
158	173	Hodgkin's disease.....	2	83	+37	0.29	57.8	Sympathetico tonic	10	19.2	11.3	13	0	28	0
144	174	Pellagra.....	1.79	90	-3.7	0.5	54.4	Sympathetico tonic	50	14.4	11.5	12.6	12.5	15	0
30*	175	Arteriosclerosis; cardiovascular renal condition	2.33	76	-5.9	1.05	62.5	Vagotonic	0	20	8.8	8.2	16	7.2	0
89*	176	Nervous.....	1.26	94	+6.4	0.33	55	Vagotonic	-12	18	14	11.8	19.6	15.4	12.4
163	163	Averages and totals.....	1.80	76	7.6	0.77	53.9	10 S., 8 V.	15	1.55	10.9	11.6	9.9	14.3	3.7

* One of group of 100 "normal" men.

TABLE 37.—The Results of Examinations of the Twenty Persons with the Highest Weight/Length Ratios

Individual Number	Weight/Length Ratio	Diagnosis	K / Ca Ratio	Sugar, Mg.	Basal Metabolic Rate	Skin Resistance to Electric Current	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Morphine, Wheal, Mm.	Morphine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
45*	317	Increased blood pressure (above 140).....	1.45	77	20	0.28	Vagotonic	-3	20.4	9.8	14.2	21.4	16.4	12
6	300	Arteriosclerosis; myocarditis	1.50	70	22	0.30	Vagotonic	0
121	294	Arthritis deformans	2.27	74	11	0.28	Vagotonic	-13	26	5.6	10.2	8.9	8	0
103*	270	Arteriosclerosis; myocarditis	1.83	57	2	0.30	Vagotonic	-1	22.4	9	12.2	18.2	12.2	0
138	270	Myocarditis; Fröhlich's syndrome.....	1.88	83	8	0.07	Vagotonic	0	23	9.5	12.5	8.7	17	6.5
93*	267	Myocarditis; hay-fever	3.22	70	0	0.25	Sympathetico-tonic	-19	20.4	8.6	12.4	15	10	0
119	266	Adenoma of the thyroid.....	2.1	73	34	0.08	Sympathetico-tonic	+13	24	5	12	11.2	12	7
107*	265	Arteriosclerosis; myocarditis	2.3	60	-6.5	0.33	Vagotonic	1	20.8	5.8	8.6	11.2	13.4	6.2
70*	264	Arteriosclerosis; arthritis deformans.....	1.45	67	23	0.30	Vagotonic	-6	18	11	9.8	13.2	10	0
123	263	Arteriosclerosis; carcinoma of the thyroid.....	2.17	81	46	Vagotonic	-3	20	6.8	11.2	10.2	10	12.2
47*	260	Healed tuberculosis	2.51	72	34	0.13	Vagotonic	-5	21.6	5.2	14.2	10.8	9	0
83*	258	Normal	2.31	68	-7	0.16	Vagotonic	+9.6	17.2	9.2	9.2	20.8	13.4	11
69*	257	Arteriosclerosis; myocarditis	1.82	67	1.3	0.37	Sympathetico-tonic	+37	20	9.2	13.6	16.6	10.2	0
54*	256	Myocarditis	80	-3.4	0.26	Sympathetico-tonic	+66	21.2	10.4	11	18	12	0
37*	254	Normal	2.26	75	-24.4	0.34	Vagotonic	-8	20.4	21.6	18	15.2	10	0
39*	254	Syphilis	1.91	79	13.1	0.29	Vagotonic	+17	18	9.8	13.8	21.8	7.6	5
59*	252	Normal	1.83	85	-6.5	0.16	Vagotonic	+2	22	7.2	9.2	21.4	15.6	8
165	250	Arteriosclerosis; glaucoma	1.79	80	0.5	0.18	16.8	13	10	14.5	12.5	0
129*	249	Tuberculosis	1.63	83	+28	0.23	Vagotonic	-10	18.4	7	10.6	9.3	12.2	0
56*	247	Tuberculosis	2.32	65	+17.9	0.32	Vagotonic	+14	17.2	5.8	10.8	22.4	13.4	7
265.6		Averages and totals.....	2.06	73.4	9.3	0.25	15 V., 4 S.	6.2	19.8	8.9	11.7	15.4	11.8	3.9

CHOLESTEROL

The determinations of cholesterol were made on 109 members of the groups of "normal" persons and patients, the average amount for the persons of the "normal" group being 207 mg.

In chart 15 we illustrate this material. Of the actually normal persons, we have only eight for consideration, and have placed the normal range at from approximately 160 to 245. Of this group, patient 92 falls far outside this range, having a cholesterol level of over 300.

Furthermore, it appears that the group with the higher levels of cholesterol includes more persons with roentgenologic evidence of

TABLE 38.—*The Results of Examinations of the Twenty Persons with the Highest Values of Cholesterol*

Individual Cholesterol, Mg.	Diagnosis	Reaction to Epinephrine
95 318	Healed tuberculosis.....	Sympatheticotonic
148 317	Vitiligo; glaucoma.....	Vagotonic
94 308	Normal.....	Vagotonic
111 290	Cardiovascular renal condition.....	Sympatheticotonic
14 278	Cardiovascular renal condition.....	Vagotonic
75 278	Cardiovascular renal condition.....	Vagotonic
100 269	Neurosis.....	Vagotonic
141 267	Glaucoma.....	Vagotonic
173 267	Tumor of the cord.....	Sympatheticotonic
61 264	Cardiovascular renal condition.....	Vagotonic
62 256	Cardiovascular renal condition.....	Vagotonic
167 256	Glaucoma.....	Sympatheticotonic
107 256	Cardiovascular renal condition.....	Vagotonic
132 256	Eczema.....	Vagotonic
71 256	Cardiovascular renal condition.....	Vagotonic
136 256	Pellagra.....	Sympatheticotonic
115 247	Cardiovascular renal condition.....	Vagotonic
127 247	Cardiovascular renal condition.....	Sympatheticotonic
150 247	Glaucoma.....	Vagotonic
73 247	Syphilis.....	Vagotonic
Average..... 208	Total.....	6 S., 14 V.

healed parenchymal tuberculosis. In connection with the group with cardiovascular renal lesions, the outstanding fact seems to be that there are more persons with arteriosclerosis in the group with the high levels of cholesterol. This seems true for the 100 "normal" men, as well as for all the persons examined.

In tables 38 and 39, we have tabulated the results of some examinations of the twenty persons with the highest and lowest cholesterol values (excluding those with exophthalmic goiter). There are obviously more persons with arteriosclerotic changes and increased blood pressure on the side of the high values of cholesterol than on the side of the low values. It appears, too, that this group includes more persons with a distinctly vagotonic reaction to epinephrine.

TABLE 39.—*The Results of Examinations Similar to Those in Table 38 of the Twenty Persons with the Lowest Values of Cholesterol*

Individual Cholesterol, Mg.	Diagnosis	Reaction to Epinephrine
124	133 Heart disease and arthritis.....	Vagotonic
108	139 Tuberculosis.....	Sympatheticonic
135	145 Nervous.....	Vagotonic
92	158 Nervous.....	Sympatheticonic
1	158 Nervous.....	Sympatheticonic
140	158 Tuberculosis; glaucoma.....	Vagotonic
169	158 Syphilis; Buerger's disease.....	Sympatheticonic
101	158 Sensitized.....	Sympatheticonic
158	163 Hodgkin's disease.....	Sympatheticonic
90	167 Cardiovascular renal condition.....	Vagotonic
84	167 Cardiovascular renal condition.....	Sympatheticonic
143	171 Pellagra.....	Sympatheticonic
85	171 Fever, unknown origin.....	Vagotonic
116	175 Urticaria.....	Vagotonic
153	175 Glaucoma.....	Sympatheticonic
152	175 Sensitized.....	Vagotonic
98	175 Cardiovascular renal condition.....	Vagotonic
139	175 Urticaria.....	Vagotonic
64	180 Normal (nervous).....	Sympatheticonic
154	180 Glaucoma.....
Average.....	102 Total.....	10 S., 9 V.

REACTIVITY TO EPINEPHRINE: THE WHEEL

The average diameter of the wheals due to epinephrine of our group of 100 "normal" men is 19.2 mm., and there appear to be relations to the calcium level, the Kromayer lamp erythema time, the basal metabolic rate, the pulse pressure and the weight/length ratio.

TABLE 40.—*The Results of Examinations of the Twenty Persons Showing the Smallest Wheals on the Intracutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Mm.	Diagnosis	Calcium, Mg.	Kromayer Light Erythema Time, Min.	Pulse Rate	Carbon Dioxide Combining Power	Ice Reaction Time, Seconds
135	12.4	Changes in capillaries; nervous.....	11.9	75	88	54.5	18
49*	12.4	Cardiovascular renal condition.....	11	330	60	50.1	15
81*	14	Cardiovascular renal condition.....	8.4	90	76	57	45
161	14	Glaucoma.....	9.17	75	88	49.4	12
77*	14	Sensitized.....	10.8	240	82	60.6	35
144	14.4	Pellagra.....	9.8	120	92	54.4	10
80*	14.8	Nervous.....	8	100	64	53.2	30
124	15.2	Arthritis.....	10.5	60	98	53.7	10
137	15.4	Glaucoma.....	8.1	130	78	51.9	30
65*	15.8	Cardiovascular renal condition.....	9.8	180	63	53.1	13
160	16	Glaucoma.....	10.86	70	68	62.7	10
87*	16	Normal.....	8.4	90	70	55.4	18
139	16	Urticaria.....	9.7	120	104	50	8
84*	16.4	Cardiovascular renal condition.....	10	90	80	53.1	20
143	16.6	Wassermann reaction +++; pellagra..	9.7	110	118	55.4	15
118	16.8	Arthritis.....	12.2	110	72	54	12
24*	16.8	Healed tuberculosis.....	11.7	120	78	53.7	20
91*	16.8	Cardiovascular renal condition.....	150	76	58.9	45
165	16.8	Glaucoma.....	10	80	110	53.9	5
167	17	Glaucoma.....	12	120	84	47.9	5
Averages	15.5	10.1	124	82	54.6	18.8

* One of group of 100 "normal" men.

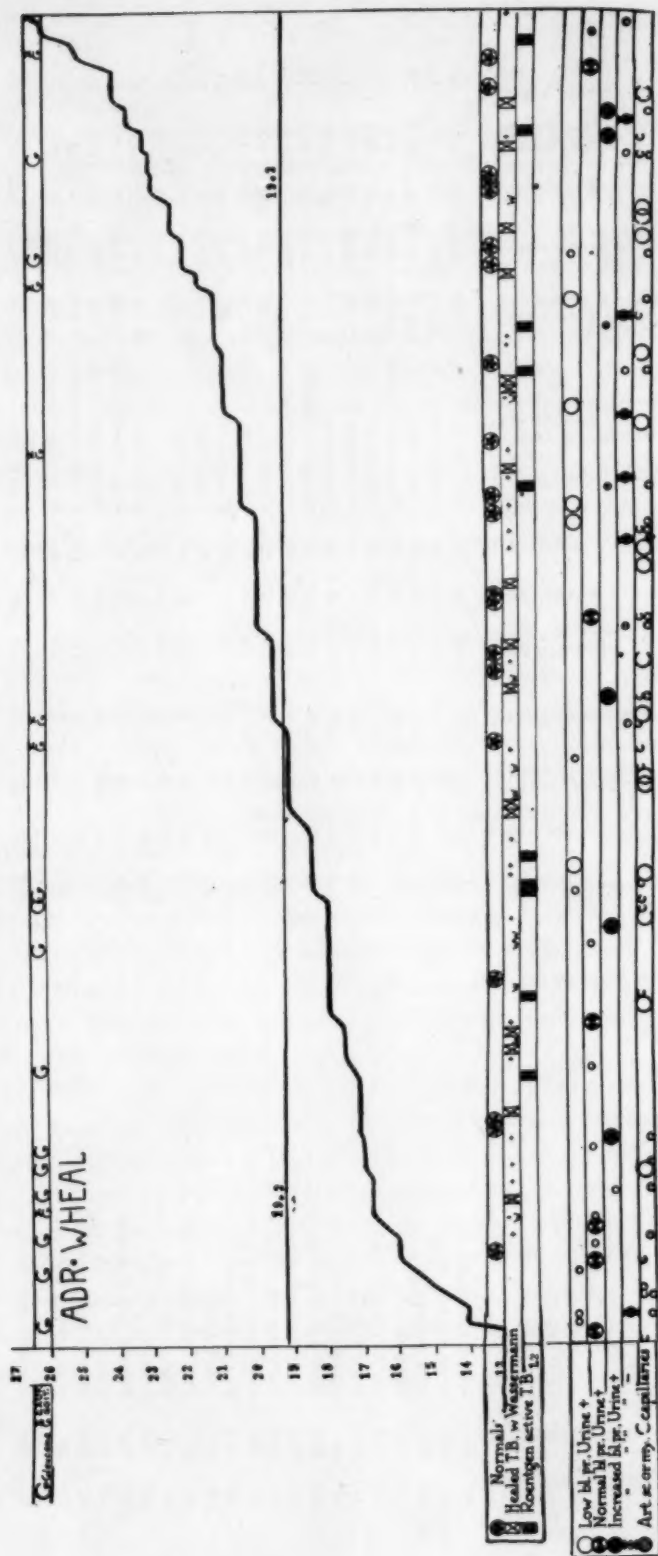


Chart 16.—The diameter of the wheal in the reaction to epinephrine of normal persons and patients with various clinical conditions.

TABLE 41.—The Results of Examinations of the Twenty Persons Showing the Largest Wheals on the Intracutaneous Injection of Epinephrine Hydrochloride

Individual Number	Epinephrine, Wheel, Mm.	Diagnosis	Calcium, Mg.	Sugar, Mg.	Kromayer Light Extinction Time, Min.	Basal Metabolic Rate	Blood Pressure, Systolic	Pulse Pressure	Pulse Rate	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	CO ₂ Combining Power	Ice Reaction, Seconds	Thyroxin, Wheel, Mm.	Thyroxin, Flare, Mm.
121	26	Arthritis deformans.....	8.9	74	120	+11	148	68	88	Vagotonic	-13	56.8	10	8	0
132	26	Angioneurotic edema.....	9.8	63	60	+4.8	120	46	80	Vagotonic	-5	63.4	15	9	8
20*	25.2	Tuberculosis.....	11.4	85	90	+30.4	130	54	80	Vagotonic	+13	62.7	15	10	2.6
50*	24.8	Normal.....	11.4	..	180	+21	128	58	67	Sympathetico tonic	+12	64.9	15	10.4	10
14*	24.4	Cardiovascular renal condition.....	11.2	67	90	+2.7	128	48	76	Vagotonic	+10	65	40	15	5
41*	24.4	Normal.....	9.8	70	75	+15	110	36	64	Vagotonic	+26	58.6	7	6.2	0
40*	24	Changes in capillaries.....	10.8	56	75	+22	110	46	60	Vagotonic	+6	55.7	40	6.2	0
96*	23.6	Healed tuberculosis.....	7.8	77	110	+23	110	44	68	Sympathetico tonic	+9	61.6	10	12	6.2
134	23.6	Cardiovascular renal condition.....	9.9	71	80	-4.4	148	62	78	Sympathetico tonic	-	54.8	12	19.2	9.6
32*	23.6	Cardiovascular renal condition.....	9.5	76	75	+22	144	58	74	Vagotonic	+22	54.1	25	9.8	0
21*	23.2	Cardiovascular renal condition.....	10.2	72	105	+4.3	140	50	72	Vagotonic	0	62.9	25	7.2	2.6
15*	23.2	Healed tuberculosis.....	12.1	70	90	-4.9	128	60	60	Sympathetico tonic	+13	57.6	38	11.6	12
102*	23.2	Tuberculosis.....	10.6	62	90	+23	114	44	96	Vagotonic	+11	60.9	40	12.2	0
138	23	Fröhlich's syndrome.....	10.6	83	90	8	122	46	80	Vagotonic	55.2	17	17	6.5
154	23	Glaucoma.....	71	90	16	194	76	70	56.6	20	26	0
35*	22.8	Normal.....	8.7	79	75	12.3	106	30	62	Vagotonic	+33	57.6	20	9.2	0
29*	22.8	Normal (bile in urine).....	10	70	105	3.5	124	46	76	Sympathetico tonic	+24	60.1	15	7.2	0
4*	22.8	Normal.....	11.8	94	120	12	114	34	80	Sympathetico tonic	+21	64.3	20	10.2	0
172	22.4	Raynaud's disease.....	13	76	105	18	108	30	94	Sympathetico tonic	+57	45	18	16
153	22	Glaucoma.....	9	83	90	2	124	64	64	Sympathetico tonic	+10	73.2	30	18	0
23.8		Averages and totals.....	10.3	74	90	11.7	125	50	74	8 S., 11 V.	+12	60	32.9	12	3.9

* One of group of 100 "normal" men.

When we include our entire material and examine the results, some of these correlations are maintained. The differences in calcium levels are not marked, but the Kromayer lamp erythema time is shortened in the group with the larger wheals and the difference between the groups in the CO_2 combining power is well marked, as is that in the ice reaction time (tables 40 and 41).

There are no apparent correlations with blood sugar level, the blood pressure, the pulse pressure or the vascular reactions to epinephrine. The pulse rate is somewhat increased in the group with the smaller wheals.

Chart 16 shows the truly "normal" persons scattered over the entire length of the curve. There appear to be no correlations with the cases of healed or active tuberculosis (roentgenologic evidence) nor with the cardiovascular renal conditions.

REACTIVITY TO EPINEPHRINE: THE FLARE

The flare from epinephrine is, as has been shown in chart 1, correlated with a number of other reactions. Thus, it is larger in persons with more calcium, more sugar, higher skin resistance, less globulin and greater vascular reaction to epinephrine. The reactions to thyroxin are not closely related, but the flare due to morphine increases with increase in the flare due to epinephrine.

These observations made on the "normal" group are all confirmed when our averages include the clinical material. In tables 42 and 43, the corresponding results are tabulated for the groups with the greatest and the smallest flares. It will be noted, among other things, that there are more persons with primarily sympatheticotonic reactions in the group with the large flares.

Chart 17 indicates that our truly "normal" group, as well as the group showing roentgenologic evidence of healed tuberculosis, are scattered over the entire curve, while more of the group with roentgenologic evidence of active tuberculosis appear at the lower end of the curve. The groups with cardiovascular renal conditions offer nothing that is characteristic, but the group with exophthalmic goiter appears to have smaller flares in contradistinction from the group with glaucoma. The "nervous" persons apparently are more apt to have large flares.

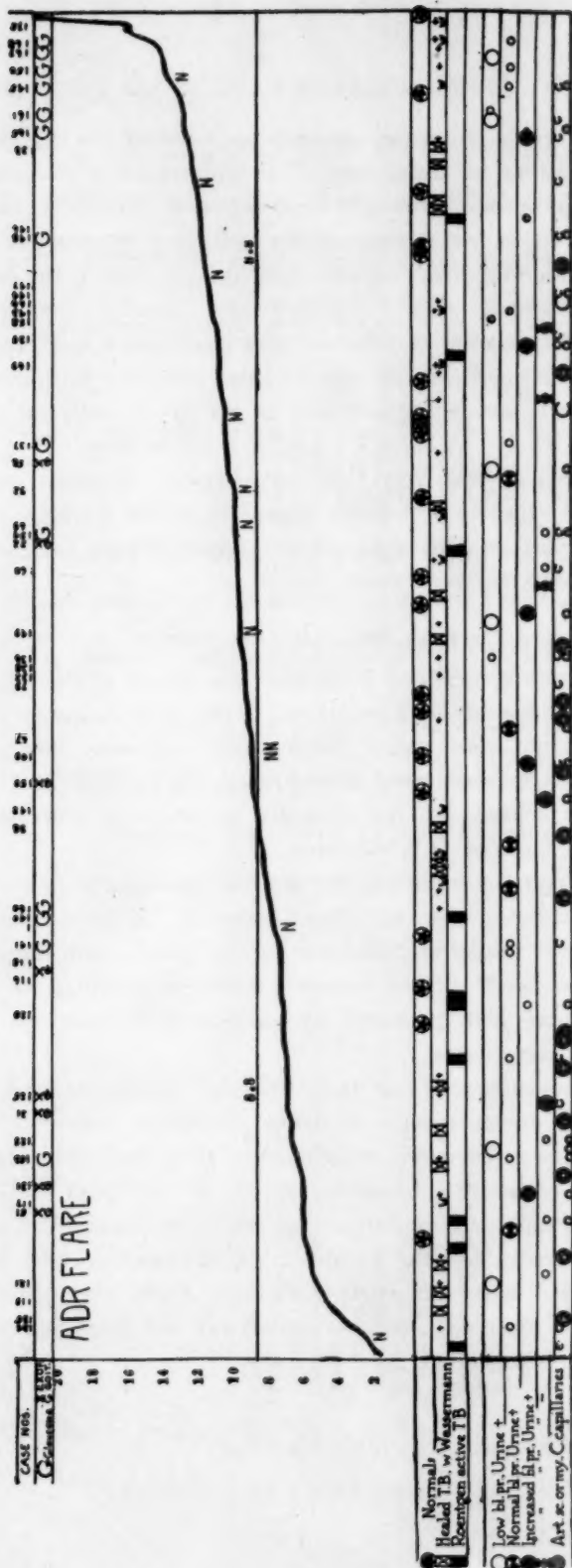


Chart 17.—The radius of the flare in the reaction to epinephrine of normal persons and patients with various clinical conditions.

TABLE 42.—The Results of Examinations of the Twenty Persons Showing the Smallest Flares Following the Intracutaneously Injection of Epinephrine Hydrochloride

Individual Number	Epinephrine, Flare, Mm.	Diagnosis	Calcium, Mg.	Sugar, Mg.	Globulin, Mg.	Skin Resistance to Electric Current	Blood Pressure, Systolic	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Morphine, Flare, Mm.
85*	1.8	Fever.....	10.6	79	33	0.41	110	Vagotonic	+19	17.2	14.2	0	13.5
108*	2.4	Tuberculosis.....	10.4	63	50	0.44	94	Sympatheticotonic	+9	18	14.8	13.2	11
194	2.6	Heart disease; arthritis.	10.5	71	40	1.05	122	Vagotonic	+2	15.2	6.8
135	3.2	Nervous.....	11.9	75	45	0.09	120	Vagotonic	-10	12.4	20	2
38*	4	Cardiovascular renal condition	8.8	63	42	0.20	136	Vagotonic	+6	20	11.2	0	2
110*	4.2	Healed tuberculosis.....	12.1	61	28	0.00	110	Vagotonic	-4	20.8	12	9.4	14.6
47*	5.2	Healed tuberculosis.....	10.4	72	40	0.13	136	Vagotonic	-5	21.6	9	0	10.8
130*	5.4	Cardiovascular renal condition	10.4	86	60	0.35	106	20	11.2	0	12.6
121	5.6	Arthritis deformans.....	8.9	74	30	0.28	148	Vagotonic	-13	26	8	0	8.8
101*	5.6	Healed tuberculosis.....	9	52	38	0.09	118	Vagotonic	20	19.6	12	10.4	16
107*	5.8	Cardiovascular renal condition	8	60	40	0.33	134	Vagotonic	-1	20.8	13.4	6.2	11.2
56*	5.8	Tuberculosis.....	9.8	65	35	0.22	124	Vagotonic	+14	17.2	13.4	7	22.8
94*	6	Normal.....	8.4	75	37	0.43	134	Vagotonic	20	20	11.2	7.8	14
14*	6.2	Tuberculosis.....	7.4	55	45	0.08	176	Vagotonic	11	20.8	12	0	10
104*	6.2	Cardiovascular renal condition	11.2	67	37	0.20	128	Vagotonic	0	24.4	15	5	7.2
117	6.2	Syphilitic arthritis.....	9.2	60	27	0.25	130	Sympatheticotonic	6	19.2	20.2	0	6.2
115*	6.2	Cardiovascular renal condition	7.8	60	60	0.28	148	Vagotonic	-4	17.2	14.2	8	13.2
81*	6.4	Healed tuberculosis.....	7.8	77	30	0.30	110	Sympatheticotonic	+9	23.6	12	6.2	12.6
95*	6.2	Cardiovascular renal condition	8.4	63	37	0.10	144	Vagotonic	+4	14	10	0	15
153	6.5	Glaucoma.....	9	83	0	0.15	124	Sympatheticotonic	+10	22	18	0	0
5.07	Averages and totals...		9.5	68	39.70	0.308	127.6	4 S., 15 V.	+4	19.5	13	4	10.5

* One of group of 100 "normal" men.

TABLE 43.—The Results of Examinations of the Twenty Persons Showing the Largest Flares Following the Intracutaneous Injection of Epinephrine Hydrochloride

Individual Number	Epinephrine, Flare, Mm.	Diagnosis	Calcium, Mg.	Sugar, Mg.	Globulin, Mg.	Skin Resistance to Electric Current	Blood Pressure, Systolic	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Morphine, Flare, Mm.
37*	12.6	Epilepsy.....	9.5	83	45	1.75	122	Sympatheticotonic	+2	20	22.2
172	16	Raynaud's disease.....	13	76	..	0.08	108	Sympatheticotonic	+57	22.4	8.5
108	16	Orthostatic albuminuria	9.4	45	13	0.16	105	Vagotonic	+4	18	0
164	14.7	Wassermann reaction +; glaucoma	8.7	65	20	0.23	110	Sympatheticotonic	+14	18	7.5
167	14.2	Glaucoma.....	12	81	27	0.85	137	Sympatheticotonic	+62	17	9
36*	14.2	Cardiovascular renal condition	12.1	90	33	0.11	104	Vagotonic	22	20.8	18
150	14	Glaucoma.....	12	82	15	0.22	140	Vagotonic	+6	17	9.5
86*	14	Nervous.....	12.6	94	40	0.36	118	Vagotonic	-12	18.8	19.6
45	13.6	Glaucoma.....	10.1	70	55	0.35	136	Sympatheticotonic	+43	18	0
41*	13.2	Normal.....	9.8	70	50	0.26	110	Vagotonic	+26	24	18.8
46*	13.2	Inanition.....	13.8	61	30	1.7	140	Sympatheticotonic	+15	21.2	16.2
161	13	Glaucoma.....	9.17	86	20	1.4	108	Sympatheticotonic	+25	14	17.5
65*	13	Cardiovascular renal condition	9.8	65	36	0.80	100	Sympatheticotonic	+30	15.8	19.8
165	13	Glaucoma.....	10	80	16	0.18	170	16.8	14.5
21*	12.6	Cardiovascular renal condition	10.2	72	20	0.74	140	Vagotonic	0	23.2	13.6
15*	12.0	Healed tuberculosis.....	12.1	70	20	0.10	128	Sympatheticotonic	13	23.2	12.4
33	21.6	Normal.....	10	75	42	0.34	116	Vagotonic	-8	20.4	15.2
24*	12.6	Healed tuberculosis.....	11.7	81	60	0.19	116	Sympatheticotonic	50	16.8	27.2
173	12.5	Tumor of the cord.....	10.5	80	6	0.00	106	Sympatheticotonic	23	21	0
80*	12.4	Nervous.....	8	60	33	1.00	116	Vagotonic	+7	14.8	19.2
13.96	Averages and totals.....		10.7	74	30	0.562	121.5	11 S., 8 V.	+20	19	13

* One of group of 100 "normal" men.

REACTIVITY TO THYROXIN: THE WHEEL

The size of the wheal due to thyroxin, as has been shown in table 1, is related to the inflammatory index, to the potassium level and to the K/Ca ratio, as well as to the amounts of the globulins.

When we examine the inclusive material, we find these conclusions confirmed, as becomes evident from a survey of the results of the examinations in twenty cases of the smallest and twenty of the largest wheals (tables 44 and 45).

Chart 18 shows the wide range of the purely normal as well as of the groups with roentgenologic evidence of healed tuberculosis, but also makes evident the fact that the groups with roentgenologic evidence of active tuberculosis are apt to have the larger wheals.

The cardiovascular renal groups show no clear-cut relation, unless it is that the arteriosclerotic changes have not been made apparent in those with the small wheals.

TABLE 44.—*The Results of Examinations of the Twenty Persons Showing the Smallest Wheals Following the Intracutaneous Injection of Thyroxin*

Indi- vidual	Thyroxin, Wheal,		Inflam- matory	Potas- sium,	K / Ca	Globulin,
Number	Mm.	Diagnosis	Index	Mg.	Ratio	Mg.
49*	4.2	Cardiovascular renal condition.....	11	25.2	2.29	17
116	5	Urticaria.....	17	19.4	1.94	40
33	5.4	Epilepsy.....	10	26.1	2.73	45
64*	6.2	Nervous.....	10	16.0	1.84	22
41*	6.2	Normal.....	9.1	21.2	2.16	50
40*	6.2	Changes in capillaries.....	6.6	18.7	1.73	44
90*	6.2	Nervous.....	7.6	14.5	1.34	33
3*	6.4	Healed tuberculosis.....	11.1	16.7	1.47	23
24*	6.6	Healed tuberculosis.....	11.6	24.8	2.12	60
26*	7.2	Syphilis.....	11	26.6	2.61	35
20*	7.2	Normal (bile in urine).....	10.7	23.9	2.30	50
23*	7.2	Healed tuberculosis.....	11.1	28.6	2.10	..
21*	7.2	Cardiovascular renal condition.....	9	25.6	2.51	20
34*	7.2	Changes in capillaries.....	7.7	27.7	2.30	25
28*	7.4	Healed tuberculosis.....	10.6	24.1	2.19	42
36*	7.4	Cardiovascular renal condition.....	7.2	26.3	2.17	33
30*	7.6	Syphilis.....	5.8	18	1.91	43
48*	8	Syphilis.....	9.7	27.6	2.37	40
121	8	Arthritis deformans.....	11.5	30.2	2.27	30
79*	8.2	Ulcer.....	5.7	20	1.78	50
Averages	6.75		9.7	22.5	2.17	36.9

* One of group of 100 "normal" men.

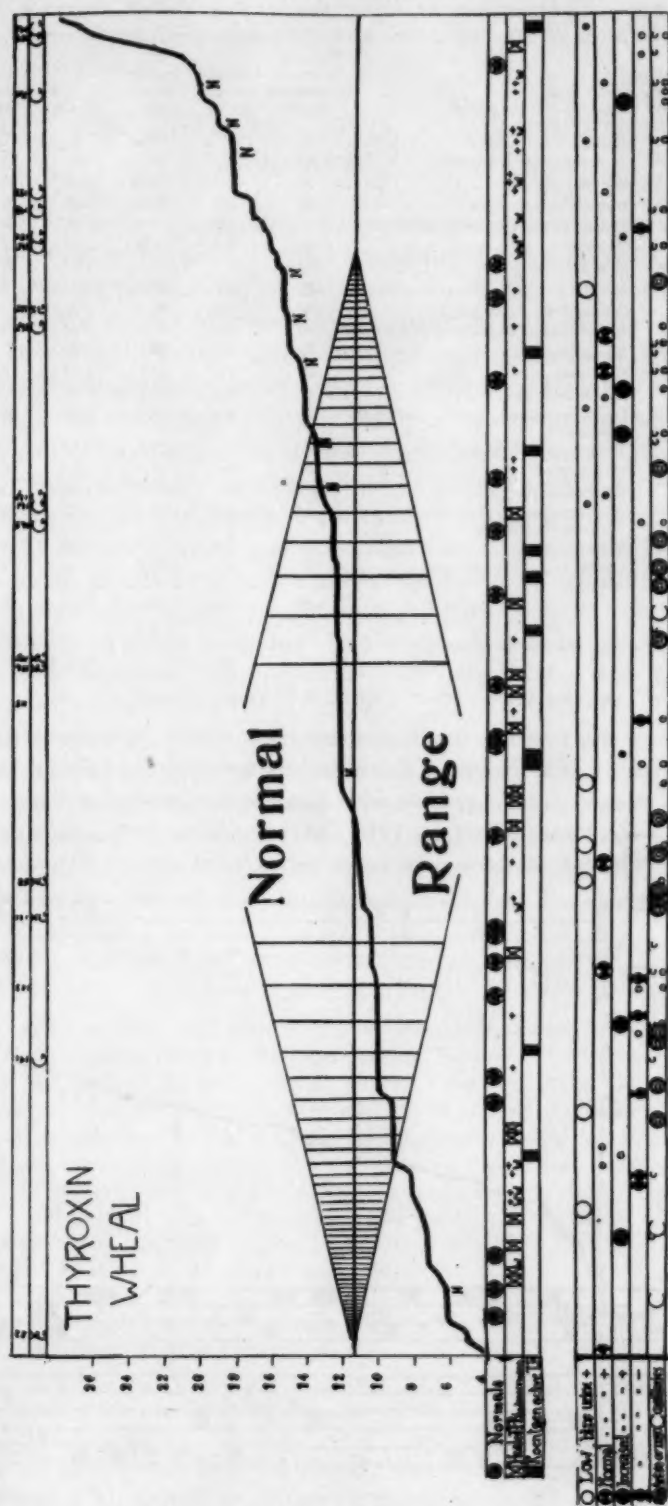


Chart 18.—The diameter of the wheal in the reaction to thyroxin of normal persons and patients with various clinical conditions.

TABLE 45.—The Results of Examinations of the Twenty Persons Showing the Largest Wheals Following the Intracutaneous Injection of Thyroxin

Individual Number	Thyroxin, Mm.	Diagnosis	Permeability of Capillaries Ratio	Inflammatory Index	Potassium, Mg.	K / Ca Ratio	Globulin, Mg.
158	28	Hodgkin's disease.....	61	4	18.53	2	17
140	27	Tuberculosis; glaucoma.....	68	4	20.7	2.6	37.5
154	26	Glaucoma.....	60	4	23.08	3
13*	22.6	Healed tuberculosis.....	64	8	23.8	2.48	20
60	21	Cardiovascular renal condition....	17.5	1.53	40
17*	20.6	Normal.....	66	8.2	18.2	1.43	17
117	20.2	Syphilitic arthritis.....	61	10	17.5	1.8	27
135	20	Nervous.....	84	14	19.6	1.65	45
160	20	Glaucoma.....	66	4.4	21.58	1.98	44
134*	19.2	Cardiovascular renal condition....	60	4	15.4	1.56	42
146	19	Myasthenia.....	75	5	14.4	1.56	32
149	19	Nervous.....	54	5.4	17.4	1.74	0
172	18	Raynaud's disease.....	72	6	21.3	1.64
136	18	Cardiovascular renal condition; pellagra	74	5	18.8	1.88	35
173	18	Tumor of the cord.....	57	8	21.3	1.57	6
166	18	Eosinophilia.....	57	8	20.6	2.27	8
171	18	Urticaria.....	64	10	21.37	1.68
169	18	Wassermann reaction +++; Buerger's disease	62	4.1	19.24	1.56	20
153	18	Glaucoma.....	70	5	18.7	2.08	0
138	17	Pröhlh's (?) syndrome.....	73	12	19.9	1.88	11
Averages	20.2		66	6.7	19.88	1.86	25.2

* One of group of 100 "normal" men.

REACTIVITY TO THYROXIN: THE FLARE

In seventy-five persons, the intracutaneous injection of thyroxin produced no flare. This group includes the majority of the persons with glaucoma (eleven). Among those with flares, the "nervous" persons are numerous. No tables based on extremes have been prepared because of the large number of those with negative reactions (chart 19).

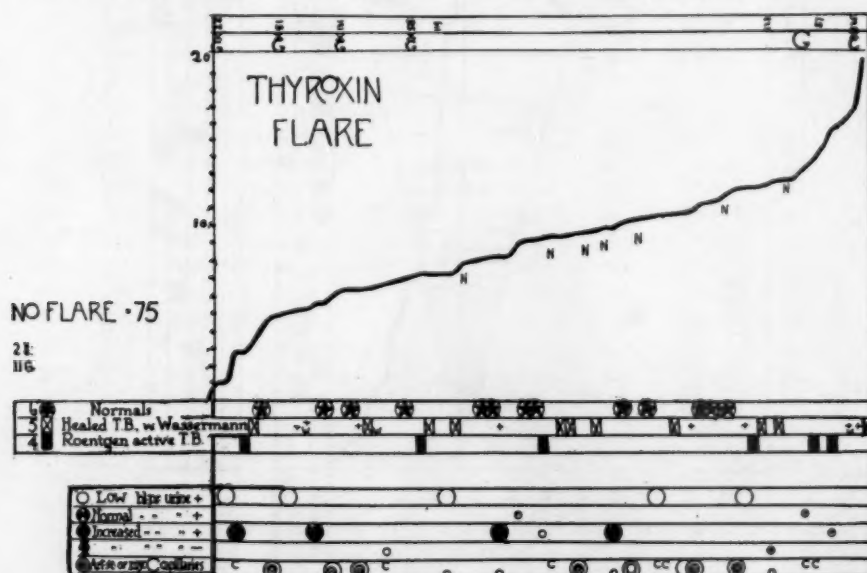


Chart 19.—The radius of the flare in the reaction to thyroxin of normal persons and patients with various clinical conditions.

IV. THE PATIENT WITH EXOPHTHALMOS AND THE NERVOUS PATIENT *

In a previous communication, we called attention to the fact that the blister time of the patient with exophthalmos is considerably shortened, and that the permeability of the capillaries of the skin, as measured by the relative amount of protein in the blister, is markedly increased.¹

It is a well known clinical observation that the skin of the patient with exophthalmos is thinner and more transparent than that of a normal person, and vasomotor lability is plainly evidenced by the rapid flushing and pallor. The arterioles, as well as the capillaries, are dilated. The functional status of the skin is one of exaggerated activity involving both the radiation of heat and evaporation. It has recently been shown that the secretory activity of the sweat glands of the skin is controlled by a skin plexus largely independent and locally autonomic, although the sympathetic nerves are commonly regarded as the nerves having to do with secretory functions. We have used the term parasympathetic status to designate this condition of activity of the skin for reasons discussed elsewhere.²

Among our group of patients there have been twelve with typical exophthalmos, as well as one patient with hyperthyroidism associated with carcinoma of the thyroid, and one patient who was being treated with thyroid extract (basal metabolic rate + 31) following a thyroidectomy. In six of the patients, we were able to carry out a complete reexamination several months after the thyroidectomy.

CLINICAL HISTORIES OF "SYMPATHETICOTONIC" PATIENTS AND PATIENTS WITH EXOPHTHALMOS

CASE 9.—A white man, aged 36, had become ill with palpitation and tachycardia fourteen months previous to the examination. He had lost 10 pounds (4.5 Kg.). Eight months later, he had a similar attack. Occasionally, he had night sweats. He had a rather coarse tremor. On exertion he showed slight dyspnea. At the time of examination, he had the papular and pustular lesions of acne. The conjunctivae were slightly injected. A few cervical glands were palpated below the angle of the jaw, and there was a light contraction of the superclavicular fossa. The blood pressure was 132 systolic and 86 diastolic. The basal metabolic rate on December 24 was + 34, and on December 28 was + 49. There was no exophthalmos. In this case, the disease was mild.

* In collaboration with Dr. Lindon Seed of the Department of Surgery, University of Illinois College of Medicine.

1. Petersen, W. F.: Permeability of Skin Capillaries in Various Clinical Conditions, *Arch. Int. Med.* **39**:19 (Jan.) 1927.

2. Petersen, W. F., and Müller, E. F.: Splanchnoperipheral Balance During Chill and Fever, *Arch. Int. Med.* **40**:575 (Nov.) 1927.

CASE 11.—A white man, aged 46, had been nervous, with tachycardia and sweating for the past eight months. He had a tremor, and was dyspneic. He had been irritable for about a year. There was no exophthalmos. The pulse rate was 80; the blood pressure was 120 systolic and 60 diastolic. His normal weight was 176 pounds (79.8 Kg.); at this time it was 136 pounds (61.7 Kg.). The neck showed a soft fullness in the region of the thyroid gland. The presence of exophthalmos was questionable. The heart seemed to be heaving somewhat, but no murmurs were apparent. The x-ray diagnosis was myocarditis. The urine was normal. The basal metabolic rate was +42. In this case, the disease was mild.

CASE 16.—A white man, aged 33, had been sick for ten months. His illness had begun with nervousness, tremor, fatigue, palpitation and occasional nausea. At the time of observation, the patient was feeling better, but still had some dyspnea. His normal weight was 152 pounds ((68.9 Kg.); at the time of the examination it was 124 pounds (56.2 Kg.). The pulse rate was 90; the blood pressure was 133 systolic and 70 diastolic. He showed no exophthalmos. The thyroid gland was diffusely enlarged. A systolic murmur was heard over the aortic valve. A trace of albumin was found in the urine. The basal metabolic rate was +20. Clinically, the case was debatable. The results of the laboratory examinations were also doubtful. The albumin/globulin ratio was high (5.6), and there was a possibility of tuberculous activity in the right apex that would account for some of the symptoms.

CASE 22.—A white man, aged 58, had become ill, three months previous to examination, with tremor, palpitation, nervousness, loss of strength and excessive perspiration. The blood pressure was 134 systolic and 64 diastolic. There was no exophthalmos. A moderately large diffuse thyroid gland of firm consistency was noted. The urine was normal. The basal metabolic rate was +44. The pulse rate was 100. The x-ray diagnosis was: heart, large; mitral lesion (?). In this case, the disease was mild.

CASE 119.—A white woman, aged 43, had felt a marked general weakness for two years; she perspired easily. During this time she had lost 20 pounds (9 Kg.), despite a good appetite. She had a slight enlargement of the thyroid gland. At the time of the first examination, the basal metabolic rate was +13 and the pulse rate 82. In addition to the endocrine disturbance, she gave some evidence of having arthritis deformans (x-ray diagnosis). No exophthalmos was observed. In this case, the disease was mild.

CASE 31.—A white woman, aged 42, began to have a swelling of the thyroid two years previous to examination. At the times of menstruation she had nausea and vomiting with increased hemorrhage. The illness had commenced with nervousness, after the birth of her sixth child, and had been particularly accentuated during her seventh pregnancy. She had diarrhea occasionally, and tremor. She had lost 44 pounds (20 Kg.) in the last ten months. Her normal weight was 175. Her weight at this time was 138 pounds (62.6 Kg.). She had a nervous breakdown three weeks before examination. The blood pressure was 115 systolic and 75 diastolic. No exophthalmos was observed. The thyroid gland was soft and the right lobe and the isthmus were particularly enlarged. The urine was normal. The basal metabolic rate on January 27 was +73, and on January 31, +44. In this case, the condition was moderately severe.

CASE 51.—A white woman, aged 58, had become ill four months prior to examination, with a loss of 50 pounds (22.7 Kg.) in weight, nervousness, the sensation of warmth and palpitations. She had vomited occasionally, and had had diarrhea. There was slight exophthalmos and the thyroid gland was moderately enlarged. A tremor was present. The urine was negative. The basal metabolic rate on

February 19 was + 67. The blood showed a sugar value of 120 mg., a nonprotein nitrogen value of 32 mg., and a urea value of 17 mg. The Wassermann reaction was negative. In this case, the disease was moderately severe.

CASE 58.—A white woman, aged 39, began to have a swelling of the thyroid gland four years prior to examination. Her illness dated back one year to a time when she grew irritable. She perspired freely and had a tremor. Exophthalmos was marked. There had been little loss of weight and the appetite was good. The goiter felt firm. The urine was normal. The basal metabolic rate was + 94 on March 23 and + 80 on March 24. The Wassermann reaction was negative. The blood sugar was 100 mg. The nonprotein nitrogen was 32 mg. In this case, the condition was moderately severe.

CASE 159.—A white man, aged 53, became ill in November, 1925; he felt weak, and lost 45 pounds (20.4 Kg.). After that he had periods of nervousness. Exophthalmos and tremor were noted (July, 1927) in the dispensary and a myocarditis was suspected (pulse rate, 96; blood pressure, 124 systolic and 60 diastolic; dyspnea, and diastolic murmur at the base). On August 2, the basal metabolic rate was + 42; it was the same in October, 1927, when we made our examination. At this time the patient was improving.

CASE 125.—A white woman, aged 29, began to be ill, eleven months prior to examination, with palpitation, weakness, loss of 57 pounds (25.9 Kg.) in weight, nervousness and excessive perspiration. The illness in question began with nausea and vomiting. Exophthalmos was present. There was a diffuse, soft enlargement of the thyroid gland. The urine was normal. The basal metabolic rate on July 2 was + 58; on July 23, + 85, and on July 27, + 59. The blood pressure was 170 systolic and 85 diastolic. The pulse rate was 140. This was a severe case.

CASE 126.—A white man, aged 21, began to be ill, four months prior to examination, with nervousness, tremor and loss of strength. His normal weight was 157 pounds (72.1 Kg.) and he had lost about 20 pounds (9 Kg.). He felt weak and perspired freely. The blood pressure was 142 systolic and 60 diastolic; the pulse rate was 112. There was moderate exophthalmos and diffuse general enlargement of the thyroid. The urine was normal. The basal metabolic rate on July 2, 1927, was + 25. The sugar was 83 mg.; the nonprotein nitrogen, 37 mg. This was a severe case.

CASE 131.—A white woman, aged 59, began to be ill, sixteen months prior to examination, with nervousness. She had a nervous breakdown one year before examination, together with palpitation and the feeling of warmth, occasional vomiting and diarrhea. Her loss in weight had been 80 pounds (36.3 Kg.), i. e., from 204 to 118 pounds (92.5 to 53.5 Kg.). There was a moderate enlargement of the thyroid gland and slight exophthalmos. The urine showed a trace of albumin. The basal metabolic rate on July 15 was + 88. In this case, the disease was severe.

CASE 57.—A white woman, aged 38, commenced being ill with palpitation six months before examination. For three months prior to examination she had been nervous and weak, had perspired readily and had lost 40 pounds (18.1 Kg.). She had been nauseated for about two months. Exophthalmos was not marked. The urine was normal. The basal metabolic rate was + 150. A goiter had been removed three months previous to examination. About Jan. 1, 1927, the patient began to feel weak and noticed lacrimation, impaired vision and slight swelling of the face. The patient returned on March 7 with some evidence of myxedema. She was given a course of treatment with thyroid extract. Our examination was made on February 22; at this time, the effect of the thyroid extract was apparent in a basal metabolic rate of + 31.

TABLE 1.—Results of Correlative Examinations

	Individual Number	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure × Pulse Rate, %	CO ₂ Combining Power	Endothelial Reaction
Mild	9	5.5	71	13	11.5	23.5	2.04	28	1.7	+49	0.75	2.2	..	140	70	90	+28	+46	61.5	+
	11	5	70	14	10.9	24.1	2.21	32	3	..	3	+42	0.14	5.5	..	124	74	108	+9	58.1
	16	5	80	16	11.4	21.6	1.9	75	5.6	..	2.25	20.8	0.11	1.9	+	150	68	88	22	35	55.3	..
	22	6	73	12	12.1	18.2	1.5	91	1.25	44	0.17	3	..	144	74	92	+31	+44	52	+
	119	6.45	58	8.5	9	18.7	2.1	75	1.7	..	1.25	34	0.08	3	..	142	82	98	+13	+24	55.4	..
Mod. severe	31	5.5	70	12.7	9.5	0.28	+73	115	75	114	49.2	..
	51	5	77	14	10	25.8	2.53	91	5.4	..	Did not appear	+67	0.13	5	..	124	50	104	25	35	55	..
	58	5	75	15	12	25.9	2.5	129	1.2	..	1.10	+43	0.10	144	60	127	+2	+5	52.9	..
	159	5	69	14	8.23	17.9	2.17	71	No globulin	..	1.18	+46	0.23	...	Trace	132	68	80	+17	+30	54.8	..
Severe	125	6	74	12	11.5	81	0.66	..	1.5	59	0.48	1.5	..	170	85	140	55.5	+
	126	6	9	18	2	77	2.3	..	?	105	0.20	0.8	?	148	66	90	20	23	60.6	..
	131	5	77	15.4	9.6	18	1.87	113	1	..	2	+88	0.21	...	+	44.6	..
	57	7.75	80	10.3	24.7	92	2.3	..	2.15	+31	0.55	94	61	78	+34	+50	60.2	..
	123	9.25	74	8	9.2	20	2.17	81	2.4	..	?	+48	2.2	+	165	100	81	-3	+5	52.4	+
Av.	5.89	72.9	12.68	10.3	21.4	2.09	79.7	2.6	1.77	+48	0.25	2.79	..	140	72	100	+19	+33	54.5	..

TABLE 2.—Comparison of the Averages of the Reactions of a Group of Patients Men, a Group of "Sympatheticotonic" Persons

Group	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Kromayer Light Erythema Time, Min.	Ice Reaction Time, Seconds	Skin Resistance	Intracutaneous Reactions to Pharmacologic Substances							
							Epinephrine Wheel (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheel (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheel (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheel (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
20 normal men.....	6.8	62	9.3	110	14.5	0.33	21	9.36	11.7	16.3	11.6	5.45	17.9	3
6 patients with exophthalmos, before operation....	5.3	75	14	110	19	0.13	21.9	8.4	10.7	13	10	7.6	13.6	0
after operation.....	7.4	62	10.7	70	9	0.23	20	12.5	13.5	7	17	1.3	16	6.5
10 "sympatheticotonic" persons.....	7.7	69.1	9	103	23	0.41	19.4	9.4	10.6	13.2	12	4	21.2	2.6
12 "nervous" patients.....	7.5	69.1	9.2	112	20.4	0.79	18.3	10	11.6	14.6	14	6.8	18.6	3.8

of Patients with Exophthalmic Goiter

Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine Wheal (Diameter, Mm.)	Epinephrine Flare (Radius, Mm.)	Morphine Wheal (Diameter, Mm.)	Morphine Flare (Radius, Mm.)	Thyroxin Wheal (Diameter, Mm.)	Thyroxin Flare (Radius, Mm.)	Caffein Wheal (Diameter, Mm.)	Caffein Flare (Radius, Mm.)	Diagnosis
Asthenic	+	Granulation	..	27	200	
Asthenic	Healed	0	Normal	..	46	195	Myocarditis (x-ray diagnosis)
Asthenic	?	+	Normal	7	33	195	7.2	18	Possibility of active tuberculosis of right apex (healed tuberculosis) (x-ray)
Nervous	Healed	+	+	5	38	233	...	26.4	10.2	15	10	5	1	7	0	Heart large; mitral lesion (x-ray)
Nervous	Normal	10	43	260	330	24	5	12	11.2	12	7	17.4	5.6	Arthritis deformans (x-ray)
Nervous	0	Normal	..	42	200	...	21.6	7	9	13.6	7.2	...	7.4	3.6	
Sthenic	Normal	5	58	195	...	19.2	6.2	11	13.4	9.2	4.8	9	...	
Asthenic	Normal	25	29	188	...	19.6	10.4	9.8	13.8	11.2	6.8	12	...	Myocarditis (x-ray) ?
Sthenic	7	53	196	158	25	9	6.4	3.5	12	0	15	0	
Sthenic	Healed	+	Normal	18	29	...	190	22.4	7	10.4	9	15.2	17	26.4	...	Myocarditis (right lung, increased fibrosis) (x-ray)
Sthenic	Normal	5	21	174	190	19.6	7	12	...	32.4	...	
Sthenic	+	Normal	7	59	177	147	16.8	6.2	12	8.8	10.4	6.2	10	...	
Sthenic	+	Normal	6	30	221	...	18.4	7.4	12.4	15.4	12.2	14	20.2	5	Hyperthyroidism; on extract after operation
Sthenic	+	Normal	8	68	203	171	20	6.8	11.2	10.2	10	11.2	19.2	...	Hyperthyroidism with carcinoma of the thyroid gland; aortitis
.....	8.6	42	208	197.6	21.2	7.5	10.6	11.5	10.6	6.4	16	2.8	

with Exophthalmos with the Averages of the Reactions of a Group of Normal and a Group of "Nervous" Persons

Blood Chemistry					Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure x Pulse Rate, %	Blood Pressure		Pulse Rate	Basal Metabolic Rate	Weight/Length Ratio	Age
Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	CO ₂ Combining Power	Sugar, Mg.			Systolic	Diastolic				
9.7	20.3	2.1	57.6	72.8	+19.6	+23.6	116	70	68	+ 5	224	40.2
11.3	23.1	2.04	54.1	91	+17	+25	142	70	110	+46	200	39
9	18.5	2.04	63	71	+ 9	+17	123	70	85	+ 7.6	240	39
10.8	18.83	1.74	54.6	72.6	+21.4	+26.7	123	70	80	+10.4	206	52
10.8	18.8	1.74	57.8	76	+10.5	+22.5	120	64	80	+ 8.5	198	33.6

CASE 123.—A white woman, aged 68, had had a carcinoma of the uterus fifteen years previously, which was removed. Four years prior to the examination, she had had a malignant tumor of the thyroid gland, which she subsequently had had removed three times. At the time of the examination, she suffered from dyspnea caused by the growth, considerable loss of weight during recent months and some evidence of hyperthyroidism. The roentgen examination of the chest revealed a large heart and aortitis. The blood pressure was 182 systolic and 100 diastolic. The tumor was regarded as inoperable. No exophthalmos was noted. The symptoms in this case were mild.

In table 1, we have grouped the results of the various examinations carried out in these cases, the first five cases being mild, the next four moderately severe and the last group severe.

For purposes of comparison with the normal, we present in table 2 the averages for twenty normal persons, six patients with exophthalmos before and after operation, ten "sympatheticotonic"³ patients and twelve "nervous" persons.

In table 3, the individual reactions of six patients with exophthalmos before and after operation are shown.

COMMENT

Blister Time.—As previously shown,² the cantharides blister time is markedly shortened in the patients with exophthalmos. We presume that this is, in general, due to the increased parasympathetic status of the periphery. Following removal of the thyroid gland, the blister time is lengthened. Seemingly, the blister time is not necessarily related to the basal metabolic rate; for in case 123 (carcinoma with hyperthyroidism; basal metabolic rate +48), the blister time was not shortened, nor was it in case 57 (therapeutic hyperthyroidism following insufficiency due to thyroidectomy; basal metabolic rate +31). On the other hand, in case 22, thyroidectomy was followed by a considerable shortening of the blister time, despite the lowering of the basal metabolic rate to +3. The patient in this case gave other evidence of continued autonomic disturbance.

Permeability of Capillaries.—The relative amount of protein present in the blister is high in the case of exophthalmic goiter. We regard this as evidence of increased capillary permeability.⁴ It will be observed that both the "sympatheticotonic" and the "nervous group" approach the patients with exophthalmos in this respect. Following thyroidectomy, permeability is diminished in all cases. Both the hyperthyroidism associated with carcinoma and that following treatment with thyroid

3. Petersen, W. F., and Levinson, S. A.: Arch. Int. Med. 42:256 (Aug.) 1928.

4. Petersen, W. F., and Willis, D. A.: Capillary Permeability and Inflammatory Index of Skin in Normal Person as Determined by Blister, Arch. Int. Med. 38:663 (Nov.) 1926.

extract are associated with high permeability. The increase in permeability seems directly related to thyroid activity in some way, but not necessarily with the factor that is responsible for the increase in basal metabolic rate. In case 16 (in which the basal metabolic rate did not change following thyroidectomy) the capillary permeability diminished. On the other hand, in patient 119 (arthritis deformans, adenoma of the thyroid; basal metabolic rate +34) the permeability was low, but the patient had some of the symptoms of hyperthyroidism.

Calcium.—Contrary to the observation of Kylin⁵ and Leicher,⁶ we have, in general, found an increase in the calcium of the serum; the average for our twelve cases is 10.4, and for the six cases studied before and after operation the respective values are 11.3 and 9. Our results agree with those of Jacobsohn and Rothschild.⁷ Herzfeld and Neuburger⁸ reported conflicting results. Whether or not the high calcium level is partly responsible for the sympathetotonic effects we cannot state. It has been previously demonstrated that calcium is lost from the body during treatment with thyroid (Bolaffio, Tedesco and Falta⁹).

Potassium and the K/Ca Ratio.—As the potassium is increased proportionally to increase in calcium, the K/Ca ratio remains approximately at 2. After thyroidectomy, the potassium level drops with the calcium level and the ratio remains constant. At the operation, both upper parathyroids were removed, with approximately two thirds of the thyroid tissue.

Albumin/Globulin Ratio.—In severe cases there is a considerable increase in serum globulin. We doubt whether this is a specific effect, because it occurs so frequently in severe intoxications. Following thyroidectomy, the albumin again increases. In sympathetotonic persons the globulin shows a slight increase.³

Neither the change in the calcium and the potassium levels nor the change in the albumin/globulin ratio is due to changes in the concentration of the serum, for we find that the serum proteins are, if anything, more concentrated after the thyroidectomy. Similar changes were reported by Frowein.¹⁰

Kromayer Light Erythema Time.—In patients with exophthalmos, the time of the appearance of the erythema following application of the Kromayer light is somewhat shortened following thyroidectomy. This

5. Kylin, E.: Acta med. Scandinav., 1928, suppl. 19, p. 1.

6. Leicher, H.: Deutsches Arch. f. klin. Med. **141**:85, 1923.

7. Jacobsohn, M., and Rothschild, F.: Ztschr. f. klin. Med. **105**:417, 1927.

8. Herzfeld, E., and Neuburger, J.: München. med. Wchnschr. **71**:1324, 1924.

9. Bolaffio, Tedesco and Falta: Wien. klin. Wchnschr. **22**:1059, 1919.

10. Frowein, W.: Ztschr. f. d. ges. exper. Med. **24**:162, 1921.

is even markedly apparent in one patient (no. 51) in whom no erythema appeared before operation, but after operation it appeared in 100 minutes.

Reaction to Ice.—The shortness of the Kromayer light erythema time is paralleled by the rapidity of the appearance of erythema following the local application of ice. Possibly, the lessening of the peripheral sympathetic tonus accounts for the more rapid reaction, although the so-called "parasympathetic" person shows little difference from the "sympathetic" person in this reaction.³

Resistance of Skin to Electric Current.—A rather striking difference exists in the resistance of the skin to electric current. This is somewhat reduced in exophthalmic goiter (a similar observation was made by Richter¹¹), but after operation it returns to normal. Whether this response is modified by the enhanced sweating of the patient with exophthalmos we leave undetermined. Lueg and Grassheim¹² studied the electric condensation values of the skin. These, too, are altered in exophthalmic goiter.

CO₂ Combining Power.—The CO₂ combining power is slightly lowered before, and returns to a supernormal level after thyroidectomy. This is in agreement with the determinations of Hollo and Weiss,¹³ Morros¹⁴ and Walinski and Herzfeld.¹⁵

Intracutaneous Reactions to Pharmacologic Substances.—The reactions of the skin to pharmacologic substances are of some interest. As compared with the reaction of a normal person, the wheal due to epinephrine hydrochloride in a patient with exophthalmos is somewhat increased and the flare lessened; the wheal and the flare due to morphine are diminished; the wheal due to thyroxin is diminished, but the flare is increased; the wheal and the flare due to caffeine are diminished. After operation there is a distinct reversal in the reaction to epinephrine in that the wheal is again diminished, but the flare increased. In the reaction to morphine, the wheal is again increased, but the flare is decidedly contracted, the same being true in the reaction to thyroxin. That these changes are associated with hyperthyroidism and not necessarily with the associated autonomic changes which are by some assumed to underly the pathologic alterations seems indicated from the reactions

11. Richter, C. P.: Electrical Skin Resistance; Diurnal and Daily Variations in Psychopathic and in Normal Persons, *Arch. Neurol. & Psychiat.* **19**:488 (March) 1928.

12. Lueg, W., and Grassheim, K.: *Klin. Wchnschr.* **7**:647, 1928.

13. Hollo, I., and Weiss, S.: *Klin. Wchnschr.* **3**:163, 1924.

14. Morros, J. S.: *Arch. Endocrinol.* **4**:279, 1926.

15. Walinski, F., and Herzfeld, E.: *München. med. Wchnschr.* **73**:2153, 1926.

TABLE 3.—*The Results of Correlative Studies of Six Patients with Exophthalmos Before and After Thyroidectomy**

Case	11	16	22	51	58	125	Averages
Blister Time, Hours							
Before operation	5	5	6	5	5	6	5.3
After operation	7.5	5.5	2.5	10	6.5	12	7.4
Permeability of Capillaries, per Cent							
Before operation	70	90	73	77	75	74	75
After operation	66	66	66	60	58	60	62
Inflammatory Index							
Before operation	14	16	12	14	15	12	14
After operation	8.5	12	25	6	8	5	10.7
Kromayer Light Erythema Time, Min.							
Before operation	180	135	75 Did not appear		75	90	110
After operation	58	60	66	100	90	66	70
Reaction to Ice, Seconds							
Before operation	?	7	5	40	25	18	19
After operation	25	7	10	10	9	10	9
Skin Resistance							
Before operation	0.14	0.11	0.17	0.13	0.1	0.48	0.13
After operation	0.23	0.5	0.11	0.11	0.18	4.4	0.23
Endothelial Reaction							
Before operation	—	—	—	—	—	+	Unchanged
After operation	—	—	—	—	—	+	—
Epinephrine, Wheal, Mm.							
Before operation	26.4	19.2	19.6	22.2	21.9
After operation	15.2	17	18	20	18	23	20
Epinephrine, Flare, Mm.							
Before operation	10.2	6.2	10.4	7	8.4
After operation	18	12.5	13	12.5	15	10	12.5
Morphine, Wheal, Mm.							
Before operation	7.2	15	11	9.8	10.4	10.7
After operation	13	12	11	17.5	12	15	13.5
Morphine, Flare, Mm.							
Before operation	18	10	13.4	13.8	9	13
After operation	14.75	7.7	10.15	8.75	0	10.7	7.5
Thyroxin, Wheal, Mm.							
Before operation	5	9.2	11.2	15.2	10
After operation	18	9	22	24	17
Thyroxin, Flare, Mm.							
Before operation	1	4.8	6.8	17	7.6
After operation	0	0	0	4.5	1.3
Caffein, Wheal, Mm.							
Before operation	7	9	12	26.4	13.6
After operation	9	21	9	24	16	25	16
Caffein, Flare, Mm.							
Before operation	0	0	0	0	0
After operation	0	0	0	10.5	0	2.5	6.5
Serum Protein, per Cent							
Before operation	7.2	7.2	7.76	7.85	8.28	9.13	7.92
After operation	8.7	6.12	8.7	7.41	8.38	9.76	8.18
Calcium, Mg.							
Before operation	10.9	11.4	12.1	10	12	11.5	11.3
After operation	8.54	9.65	9.81	?	7.76	9.6	9.07
Potassium, Mg.							
Before operation	24.1	21.6	18.2	25.8	25.9	?	23.1
After operation	17.75	20.7	20.4	19.24	13.49	19.7	18.5
K / Ca Ratio							
Before operation	2.21	1.7	1.5	2.58	2.15	?	2.04
After operation	2.08	2.14	2.08	?	1.74	2	2.04
CO ₂ Combining Power							
Before operation	55.3	52	55	52.9	55.5	54.1
After operation	57.5	66.2	74	62.2	50.1	62.6	63
Albumin / Globulin Ratio							
Before operation	3	5.6	?	0.54	1.2	0.66	2.2
After operation	No globulin	7.3	7.3	4.5	1.9	2.7
Sugar, Mg.							
Before operation	82	81	91	91	120	81	91
After operation	61	67	71	90	71	67	71
Reaction to Epinephrine:							
Increase in Pulse Pressure, per Cent							
Before operation	+0.06	+27	+31	+25	+2	?	+17
After operation	14	10	15	7	0	9	+9
Increase in Pulse Pressure x Pulse Rate, per Cent							
Before operation	0	35	44	35	5	?	25
After operation	23	17	35	16	0	13	17
Pulse Rate							
Before operation	108	88	92	104	127	140	110
After operation	84	72	80	74	90	100	86
Blood Pressure, Systolic/Diastolic							
Before operation	124/74	150/68	144/74	124/50	144/60	170/85	142/70
After operation	118/78	134/70	124/66	105/77	130/72	126/80	123/74
Pulse Pressure							
Before operation	50	82	70	74	75	85	72
After operation	40	64	58	27	58	46	49
Weight/Length Ratio							
Before operation	195	105	233	195	188	...	200
After operation	234	186	288	270	222	210	240
Basal Metabolic Rate							
Before operation	42	26	44	67	43	59	46
After operation	-3	20	3	-12.6	16.5	21	7.6

* The determinations before operation are placed in the upper line and those after operation in the lower line of each bracket.

of the skin in patient 123, which, in general, agree with the observations of the other patients with exophthalmos. This particular patient was suffering from carcinoma of the thyroid gland and not from true exophthalmic goiter, there being presumably no underlying or preceding autonomic disturbance.

PREOPERATIVE AND POSTOPERATIVE REACTIONS

When one examines table 3 showing the reactions before and after thyroidectomy, it becomes apparent that a dissociation of certain of the reactions exists.

In case 16, for instance, thyroidectomy was not followed by clinical improvement. The basal metabolic rate remained unchanged (+20), the weight diminished, the patient felt weak and a moderate tremor persisted. It will be noted that the blister time remained practically unaltered, as did the time of the reaction to ice.

The reaction of the skin to Kromayer light, the resistance to electrical current and the reaction to morphine followed the typical courses, the capillary permeability diminished and all the chemical and cardiac reactions returned toward the normal.

In case 22, on the other hand, the basal metabolic rate was lowered, and the weight of the patient increased; nevertheless, some of the reactions of the skin showed a distinct abnormality. Thus, the blister time was short, the resistance of the skin to electric current was diminished, and the reaction to morphine was reversed, the reaction to ice was prolonged and the reaction to the Kromayer light was unaltered. The permeability of the capillaries, however, showed normal diminution. Chemically, the only deviation was an increase in potassium instead of a diminution. Clinically, this patient improved.

It seems obvious that one cannot make merely an augmented secretion from the thyroid responsible for all alterations in these autonomic reactions, because if this were the only factor, all of them should return toward the normal after operation, while, as may be observed, there is sometimes a distinct difference in the reactions—for example, in one case the return of the basal metabolic rate to normal, and in the other a persisting increase in the rate.

If one now examines table 2 and compares the results of the examinations of the normal persons with the results of the examinations of the group with exophthalmos before and after operation, it becomes evident that, despite the restoration of weight, the normal basal metabolic rate and the relief of clinical symptoms, decided alterations of the reactions of the skin are still manifest. Thus, the resistance of the skin to electric current remains low; the ice reaction time and the Kromayer light erythema time are short; the red flare of the reaction to epinephrine is increased, while that of the reaction to morphine is diminished; the wheal in the reaction to thyroxin is

increased while the flare is diminished, and in some cases, the flare in the reaction to caffeine seems also increased.

CLINICAL HISTORIES OF THE NERVOUS PATIENTS

In the nervous group, our material consists of four persons from the so-called "normal" series, three medical students and a small number of persons studied in the Research Hospital. We have not sought to examine a large series of neurasthenic persons, but have merely grouped the persons who came under observation in the routine study in whom nervousness played a large rôle in the symptom complex (table 4).

CASE 80.—An electrician, an American, aged 29, had a distinct tremor and felt nervous. The onset had followed an explosion in a mine in 1924. He had had urticaria in 1922. He was a moderate smoker.

It is to be noted that: the capillaries were very permeable; the calcium level was potassium levels were low, as was the K/Ca ratio; the capillaries of the skin showed some granulation; the flares about the sites of the intracutaneous injections of pharmacologic substances were wide; the reaction to ice was delayed and faint; the resistance of the skin to electric current was high; the erythema resulting from the application of the Kromayer light was marked.

CASE 92.—A medical student, Jewish, aged 22, was nervous, sweated easily and had an occasional tremor. He suffered from lassitude and inability to concentrate. He had a bowel movement once or twice a week.

It is to be noted that: the capillaries were very permeable; the calcium level was low, while the K/Ca ratio was high; the reaction to epinephrine was strongly sympathetotonic; the flares of the reactions to pharmacologic substances were all wide, and the reaction to the Kromayer light was faint.

CASE 135.—A tailor, Jewish, aged 29, felt nervous and weak, and had had some night sweats and some loss of weight (12 pounds [5.4 Kg.] in one year). The basal metabolic rate was +17. This patient was under observation in the Research Hospital for possible exophthalmic goiter.

It is to be noted that: the capillaries showed increased permeability; the K/Ca ratio (1.8) was somewhat lowered; the globulins were increased; occasional granular casts were observed in the urine; the capillaries of the skin showed evidence of a beginning granulation and beading; the reaction to epinephrine was "vagotonic"; the flares of the pharmacologic skin reactions were diminished, and there were roentgenologic evidences of a probably healed tuberculosis.

Of these three cases, therefore, only the third gave evidences of organic disturbances (granular casts), but in all of them there was high permeability of the capillaries, as well as an alteration of the calcium level or the K/Ca ratio.

In the next four cases, a moderate increase of capillary permeability was shown.

CASE 5.—A housewife, Jewish, aged 48, the wife of patient 6, had vague pains all over the body, and was nervous.

It is to be noted that: the calcium level was high, but the K/Ca ratio was within normal limits; there was a trace of albumin in the urine, and the heart and aorta appeared large on roentgen examination.

CASE 109.—A spinster, American, aged 42, became weak after unilateral ovariectomy fifteen years prior to examination. Following this, she was nervous, had palpitation, perspired excessively and spent much time in bed because of weakness. One sister had hyperthyroidism.

It is to be noted that: the potassium level and the K/Ca ratio were outstandingly low; the basal metabolic rate of +55 was questionable, the test being unsatisfactory because the patient was extremely nervous; the pulse rate was increased; the CO₂ combining power was low; the blood cholesterol level was high;

TABLE 4.—The Results of Correlative Exam

Individual Number	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure × Pulse Rate, %
80	6	91	15.1	8	13.7	1.7	69	2	..	16.5	+13	1.6	3.8	..	116	68	64	+ 7	+12
92	9	83	8	8.4	19.5	2.32	67	2.8	..	1.5	- 0.8	0.57	2	..	110	60	72	+46	+70
135	6	84	14	10.8	19.6	1.81	75	1.2	..	1.25	+17.6	+ Casts	120	60	88	-10	-15
5	5	72	13	11.9	25.7	2.16	72.7	1.5	..	1.25	0.21	3.2	Albumin, trace	132	92	76
109	6	72	12	10.8	16.2	1.5	67	2	..	1.35	+55	0.47	100	60	88	+ 3	+16
2	7	66	9.8	12.9	26.1	2.02	74.2	3.5	-11	0.1	100	60	100
1	8	68	8.5	12.1	24.9	2	113	2	..	5	+ 7	1	132	74	80	+35	+52
90	9	60	7.6	11.4	14.5	1.34	68	2	..	1.75	- 8.3	0.44	4	..	122	54	67	+17	+40
86	15	58	3.8	12.6	15.9	1.26	94	1.5	..	1.75	+ 6.4	0.36	1.8	..	118	60	74	-12	-12
46	6	59	10	13.8	17.4	1.24	61	2.3	..	1.15	+13	1.7	2	..	140	82	76	+15	+37
149	10	54	5.4	10.1	17.4	1.72	82	?	..	1	+ 5	0.95	110	62	72	+10	+22
60	4	51	12.7	9.6	16	1.66	70	2.7	..	2	+ 4	1.9	2	..	140	48	84	0	+ 8
6	6.25	10.5	18.9	1.8	70.2	1.66	+	1.25	+29.5	0.3	4	Albumin, trace	120	60	72
Aver.	7.5	60	9.2	10.8	18.8	1.74	76	1.98	..	1.87	+ 8.5	0.79	3.5	..	120	64	80	+10.5	+22.5

the wide flare of the reaction to thyroxin was the only abnormality of the intracutaneous reactions, and the reaction to the Kromayer light was faint.

CASE 2.—A school boy, American, aged 12, had vasoneurosis and epilepsy. He showed active cardiac reflex, and marked mottling of the skin due to areas of vasoconstriction and vasodilatation. This patient is not to be considered as comparable with the others of the group, but has been, nevertheless, included because of the general interest of his case.

It is to be noted that: the calcium level was high and the K/Ca ratio normal; the Kromayer light erythema time was prolonged; the basal metabolic rate was low; the resistance of the skin to electric current was low, and the pulse rate was high. Microscopic examination of the capillaries of the skin showed marked dilatation.

CASE 1.—A medical student, Jewish, aged 23, was out of school because of a nervous breakdown. He had a tremor and felt weak.

It is to be noted that: the calcium level was high, but the K/Ca ratio was normal; the blood sugar level was high; the Kromayer light erythema time was delayed; the resistance of the skin to electric current was high; the reaction

to epinephrine was strongly positive, and the flare of the reaction to thyroxin was increased.

The remaining six patients had low capillary permeability.

CASE 90.—A mail sorter, American, aged 30, was nervous (said that he got "rattled easily"). He was sensitive to venipuncture.

A low K/Ca ratio was the only outstanding abnormality.

CASE 86.—A dentist, American, aged 50, had a "breakdown" four years prior to examination. He was suffering from alcoholism, was nervous, had lost his practice and was "down and out." Occasionally, he worked as a janitor. He had always been the most nervous one of his family. His mother had exophthalmic goiter. He had had angioneurotic edema when a student in 1900.

inations of a Group of Nervous Persons

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine Wheal (Diameter, Mm.)	Epinephrine Flare (Radius, Mm.)	Morphine Wheal (Diameter, Mm.)	Morphine Flare (Radius, Mm.)	Thyroxin Wheal (Diameter, Mm.)	Thyroxin Flare (Radius, Mm.)	Caffein Wheal (Diameter, Mm.)	Caffein Flare (Radius, Mm.)
53.2	..	Sthenic	+	Slight granulation	30	29	212	222	14.8	12.4	12.4	19.2	13.4	9	16.2	7
56.8	..	Sthenic	+	Normal	20	22	210	158	20.4	10.2	11.8	17	15.2	7.6	10	10
58.9	..	Sthenic Large	Healed Healed	+	+	18	26	183	145	12.4	3.2	8.2	1.6	20.2	0	25	0
51.4	..	Asthenic	Normal Dilated	25	42	140	267	17.4	9	9	7.2	12	9.4	16.2	0
55.6	..	Asthenic	Normal	25	23	202	158	20	8	12.4	16	13.2	9.6	12.2	0
62.1	..	Asthenic	Normal	10	30	192	222	18.4	11.6	10.4	20.2	12.2	0	27.4	0
57.9	..	Asthenic	Normal	25	50	176	185	18.8	14	11.8	19.6	15.4	12.4	14.2	0
55	..	Sthenic	Normal	25	50	176	185	18.8	14	11.8	19.6	15.4	12.4	14.2	0
56.2	..	Asthenic	+	Urinary disturbance	15	20	168	...	21.2	13.2	15	16.2	12.2	11.2	25.2	9.2
65.4	..	Sthenic	+	Normal	15	35	200	215	20	9.6	15	7.4	19	0	20	10
54.8	..	Asthenic	Healed	+	Normal	20	22	160	...	21.2	10	12.2	22	14.4	10.2	30.4	2.6
61.1	..	Asthenic	0	Normal	..	49	300									
57.8						20.4	33.6	198	196	18.3	10	11.6	14.6	14	6.8	18.6	3.8

It is to be noted that he had a prolonged blister time; a low K/Ca ratio; a high sugar level; a vagotonic reaction to epinephrine, and increased flares at the sites of injection of pharmacologic substances (except caffein).

CASE 46.—A carpenter, American, aged 29, a poorly developed person (from insufficient nutrition), fainted on venipuncture. He was nervous and had headaches frequently. This person died a few months later at the Cook County Hospital from bronchopneumonia.

It is to be noted that he had a high calcium level with a low K/Ca ratio; a high resistance of the skin to electric current; relatively high blood pressure, with some evidence of abnormality of the capillaries of the skin, and an increase in the flares of the reactions to all the pharmacologic substances.

CASE 149.—A plumber, American, aged 35, was nervous, had some night sweats and had lost some weight. Recently, he had been in financial difficulties. His mother had high blood pressure and was nervous.

It is to be noted that: The K/Ca ratio was low; the blood sugar was slightly increased; the resistance of the skin to electric current was high, and the blister time was prolonged.

CASE 69.—A medical student, Jewish, aged 22, was nervous and had a tremor. He felt weak on venipuncture. He had had a duodenal ulcer since 1925. His father was nervous, with a blood pressure of 160 systolic and 170 diastolic. His mother also was nervous, and had a blood pressure of 210, with myocardial degeneration.

It is to be noted that he had a short blister time; a low K/Ca ratio; a high resistance of the skin to electric current; an increase in pulse pressure; marked flares in the reaction of the skin to the pharmacologic substances, and well marked clinical symptoms of the systemic reaction to epinephrine—pallor, headache, feeling of distress, etc.

CASE 6.—A painter, Jewish, aged 49, was nervous, had vague pains and was occasionally dizzy, especially after eating. The blood pressure in November, 1926, was 160 systolic and 80 diastolic. There was a contraction in the visual fields indicating early optic atrophy (late neurosyphilis). The Wassermann reaction was positive. The roentgen examination of the chest indicated sclerosis of the aorta, and large heart. The patient died several months later from myocardial degeneration.

The low K/Ca ratio and an increase in the basal metabolic rate were the most prominent observations; there was a trace of albumin in the urine.

COMMENT

That the emotional states can alter the mineral metabolism was shown by Dresel.¹⁶ Tómasson¹⁷ also studied the correlation of mental excitation and the mineral balance. His studies, however, were made on psychopathic persons, as were the studies of Weston and Howard.¹⁸

When we review this small series of cases, the outstanding clinical complaint being nervousness (with the exception of case 2), the most striking observation in the blood seems to be an unusually low K/Ca ratio. Rather striking, too, is the relatively high resistance of the skin to electric current—in sharp contrast to the observations in the exophthalmic group.

On the other hand, these persons showed an increase in the red flare at the site of the injection of thyroxin, similar to that found in the patient with exophthalmos.

While the patient with exophthalmic goiter presented a fundamental autonomic disturbance, and seemingly a "thyroid factor" not necessarily associated with the same thyroid factor that increases the basal metabolic rate, the nervous patients presented mixed autonomic exaggerations, as well as varying reactions to epinephrine and an exaggeration of the flare due to thyroxin similar to that seen in the patients with exophthalmic goiter (and which is diminished after thyroidectomy). The differentiation of the so-called cases of "autonomic imbalance" from exophthalmic goiter has been discussed particularly by Kessel and

16. Dresel: *Klin. Wchnschr.* **33**:311, 1924.

17. Tómasson, Helgi: *Blodets Elektrolyter*, Copenhagen, Levin & Munksgaard, 1927.

18. Weston, P. G., and Howard, M. Q.: Determination of Sodium, Potassium, Calcium and Magnesium in Blood and Spinal Fluid in Manic-Depressive Insanity, *Arch. Neurol. & Psychiat.* **8**:179 (Aug.) 1922.

Hyman,¹⁹ and Eason,²⁰ too, has covered the subject, so that we need not dwell on it here.

We can only suggest from these limited observations that the mineral balance of the "nervous" patient is apparently altered, so that the potassium values of the serum are sometimes low. With this there appears to be an increase in the capillary permeability. That the emotional state can apparently have some influence here is made probable from the following observations:

The person examined was one of the hospital technicians, a man, aged 40, highly intelligent and normal on physical examination. He was first examined in December, 1926. At this period, his blister time was found to be six hours, and his capillary permeability 80. The pulse rate was between 68 and 72; the blood pressure was 120 systolic and 70 diastolic with a negligible effect following the injection of epinephrine hydrochloride. The basal metabolic rate was — 12.

He was reexamined in June, 1927. At this time the blister time was five hours and the capillary permeability had diminished to 64; the blood pressure had diminished to 112 systolic and 70 diastolic.

We were at a complete loss to account for the high permeability of the capillaries first noted, until a subsequent history was given us by this person to the effect that during the time of the first examination he was in the process of losing his entire savings in a stock venture and was naturally under great mental strain.

CONCLUSIONS

Observations made on a small series of patients with exophthalmos reveal the following changes: shortened blister time, increased capillary permeability, lower resistance of the skin to electric current, increased serum globulins, increased serum calcium with a normal K/Ca ratio and a lower carbon dioxide combining power.

After operation, a reversal of these reactions usually occurs.

The reactivity of the skin to injections of the pharmacologic substances reveals definite changes before and after operation, involving particularly the reactions to epinephrine, morphine and thyroxin.

From an analysis of the postoperative reactions in individual cases, we believe that factors other than those responsible for the increase in the basal metabolic rate must be considered in the exophthalmic complex.

The so-called "nervous" patients of our series appear to have an associated or underlying change in the K/Ca ratio and the group has a low potassium level. In general, the capillaries of the group are more permeable, but there are individual exceptions. They resemble the patients with exophthalmos, too, in the degree of their reactivity to thyroxin. They differ markedly in having a higher resistance of the skin to electric current.

19. Kessel, L., and Hyman, H. T.: *Am. J. M. Sc.* **165**:513, 1923; *Studies of Exophthalmic Goiter and Involuntary Nervous System; Diagnosis of Exophthalmic Goiter*, J. A. M. A. **88**:1478 (May 7) 1927.

20. Eason, John: *Exophthalmic Goiter*, New York, The Macmillan Company, 1927.

V. PATIENTS WITH GLAUCOMA AND THEIR VASCULAR REACTIONS *

During the course of work which Goldenburg¹ carried out in connection with glaucoma, the conclusion was reached that the inherent cause lies in alterations of the capillaries of the ciliary body, these alterations consisting of an increase in permeability (probably associated with an increased metabolic activity of the cells of the ciliary body) with a resulting swelling of the body, a coincident shutting of the canal of Schlemm and an increase in the pressure of the aqueous as a result of the continued production of the fluid with diminished possibilities of its proper removal. It is our opinion that these alterations may take place rapidly and particularly in persons who are constitutionally so oriented, the capillaries of the body are more labile. That the vessels of the eye may show such sudden swelling of the endothelium has been observed by Lenaz² in a case in which the endothelial occlusion in an arterial branch was so great that an embolus was suspected.

Endothelial instability is found associated with certain endocrine or autonomic disturbances, which only in recent years have been studied more intensively. In the group showing this association are included persons with urticaria, angioneurotic edema, hay-fever, asthma, migraine and mucous colitis, conditions in all of which distinct alterations may occur in the ionic equilibrium (particularly the K/Ca ratio, CO₂ combining power, cholesterol content, etc.), alterations not yet fully explainable. To this group must be added the persons with hyperpiesis, as well as the ones with hypotension—which, according to Kylin,³ are merely different clinical responses to the same basic alteration.

During the course of the study we felt it might be of some interest to examine patients with glaucoma with particular reference to the blood chemistry, the general reactions of the skin and the vascular condition (microscopic examination of the capillaries of the skin, roentgen examination of thoracic vessels, examination of the urine, etc.).

We have examined in detail fourteen patients of the Illinois Charitable Eye and Ear Infirmary. The histories of these patients are briefly

* In collaboration with Dr. Michael Goldenburg, Illinois Charitable Eye and Ear Infirmary, and Dr. Louis Parmacek.

1. Goldenburg, Michael: Illinois M. J. **52**:474, 1927.

2. Lenaz, L.: Wien. klin. Wchnschr. **39**:1015, 1926.

3. Kylin, E.: Acta med. Scandinav., 1927, supp. 19, p. 1.

set forth in table 1. In making the examinations, we have carried out the routine described in part 1.⁴

When we so analyzed our small series we found that every one presented definite evidence of alteration referable to the vascular system.

Of the two patients who had syphilis, no. 145 had distinct granulations in the capillaries of the skin, albumin in the urine and, as revealed by an x-ray picture of the chest, syphilitic aortitis; no. 164 had granular casts in the urine, and the x-ray picture revealed syphilitic aortitis.

Of the three patients who had high blood pressure, no. 154 (whose blood pressure was 190 systolic and 118 diastolic) revealed an arteriosclerosis of the aorta on roentgen examination, and granulations of the capillaries of the skin. No. 170 (whose blood pressure was 188 systolic and 96 diastolic) with a blood sugar content of 320 Mg. and a basal metabolic rate of + 33, had a pulse rate of 104, and the roentgen examination showed a definite sclerosis of the aorta. No. 165 (whose blood pressure was 170 systolic and 100 diastolic) had hyaline casts in the urine and a pulse rate of 110; roentgen examination showed an enlarged heart and a dilated aorta. The rest of the patients had blood pressure within the normal range. Of these, no. 150 had hyaline casts in the urine and gave roentgenologic evidence of pulmonary fibrosis; no. 153 had granular casts in the urine and gave roentgenologic evidence of arteriosclerosis, as well as of fluid in the chest. No. 137 had albumin in the urine, and the capillaries of the skin showed distinct dilatations. No. 140 had albumin in the urine and suffered from hay-fever; the roentgenogram of the chest indicated some activity at the right upper apex. No. 141 had albumin in the urine, and the capillaries of the skin showed marked granulations. No. 161 had albumin in the urine, and the capillaries of the skin showed marked dilatations. No. 148 gave a history of cerebral hemorrhage; the roentgenogram indicated a marked sclerosis of the larger thoracic vessels, and the capillaries of the skin showed marked granulation. No. 160 had asthma; in addition, the roentgenogram indicated a dilatation of the aorta, with arteriosclerosis, and with fibrosis and atelectasis of the lungs. No. 167 had low CO₂ combining power, in addition to the highest sensitivity to epinephrine observed in the group. The capillaries of the skin revealed no marked changes. The roentgen examination indicated an old pulmonary fibrosis and bronchiectasis.

4. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch. Int. Med.* **38**:663 (Nov.) 1926.

TABLE 1.—The Clinical Histories of Patients with Glaucoma

Case	Sex	Occupation	History of Clinical Picture	Vision	Tension Schlitz	Type	Date of Operation	Tension After Operation	Later Tension	Last Vision	Complications	
137	F	Housewife	2/3/27; pain in right eye for week; headache above orbit; lacrimation and photophobia; lids normal; conjunctiva injected; iris normal; pupil contracted; cornea cloudy and stippled; anterior chamber shallow	R. Had more at 18" L. 20/30	R. 65 L. 15	Acute congestive (or inflam- matory)	2/8/27 Iridotasis	R. 25 L. 15	R. 30 L. 17%	As before	Reoperation necessary	
140	M	Laborer	One year ago left eye was painful, but re- covered without treatment; 9 months ago foreign body in left eye—although eye was not very sore, vision was bad; 3 weeks ago eye so painful patient had to stop work; eye injected, pupil dilated, cornea steamy and insensitive; hay-fever	R. 20/25 L. No light percep- tion or pro- jection	R. 12½ L. 45%	Acute attack superimposed on chronic congestive glaucoma	8/16/27 Iridotasis	
141	F	Housewife	Trouble in left eye 3 or 4 years ago; vision gradually failed; not always painful; pain severe now and located in top of head; right anterior chamber shallow; pupil dilated and not reactive to light; marked cup; left scleral staphyloma at 12 o'clock; iris drawn into staphyloma; pupil oval and not reactive to light; anterior chamber shallow; iris cloudy; fundus invisible	R. 20/100 L. Had more	R. 30¼ L. 50¼	Chronic congestive	Trephine	24
145	M	None	Gradually falling vision for about 4 or 5 months; cataract	R. 20/100 L. Fingers at 3 feet	R. 16 L. 40	L. Noncon- gestive (simplex)	8/2/27 Iridotasis	Down to markedly improved	R. Incipient cataract, central choroiditis L. Cupping of disk	
148	F	None	Chronic glaucoma in both eyes for several years; right operated on 3 years ago, be- came worse and later enucleated; left pupil dilated; cornea steamy; vitiligo; old cere- brohemorrhage	R. Enucleated, had more	L. 32	Chronic congestive	9/6/27 Iridotasis
150	M	Teamster	Right enucleated; left hurt 3 weeks ago with iron object; became fluid in 3 days; later cleared up; later vision became foggy; some pain; slight injection of left conjunctiva; cornea and iris normal; pupil regular; ante- rior chamber shallow; deep cupping of disk	R. Enucleated, 20/50	L. 54	Noncon- gestive	3/1/27 Iridotasis; could not reduce iris with exercise	With glasses, 20/30
153	M	Farmer	Vision slowly failing for past 4 or 5 years; no pain; right pupil dilated, cornea steamy; anterior chamber shallow; left pupil dilated; anterior chamber shallow; cataract	R. Perception and projection poor with bright light L. Very poor with bright light	R. 52 L. 48	Noncon- gestive Noncon- gestive	R. 4/13 L. 9/20 Iridotasis, both eyes	11/2/27 R. 43 ? L. 52 ?	R. Central opacity of lens L. Larger central opacity of lens; transillumination negative	

154	M	Laborer	Severe pain over right eye 2 weeks ago; similar attack 2 years ago; vision good until 2 weeks ago; then it began to fall with pain in head; conjunctiva congested; some ciliary injection; cornea hazy; pupil does not react to light; anterior chamber fairly normal	R. 20/200	R. 01	Acute congestive	10/28/27 trephine	Tension went up to 83 under physostigmin and MgSO ₄ ; by proctoclysis; 11/17/27, enucleation
160	M	Laborer	"Terrible" pain over right eye; patient unable to see; asthma	R. Fingers at 4 feet L. 20/40	Acute congestive	9/12/27 deep iridectomy 10/18/27 iridectomy enlarged	9/28/27, 38	
161	F	Housewife	Vision falling for past 3 or 4 years; occasional pain on right side of head; pupil widely dilated; anterior chamber shallow and lens hazy; fundus indistinct; vessels of sclera dark, tortuous; marked cup; optic atrophy; left normal; scleral vessels dilated	R. 50 L. 20	Chronic congestive	10/18/27 iridotasis 12/6/27 iridotasis	R. 25% L. 16% 12/6/27, 7% R. 12% L. 18%	12/5/27 30 1/16/27 30 R. 12% L. 18%	
164	M	Insurance agent	Pain in last 4 months in right eye and side of head; pupil dilated; cornea hazy; anterior chamber deep	R. 42% L. Normal	Acute congestive probably secondary	9/29/27 anterior sclerotomy 11/1/27 iridotasis	11/12/27 16	Wassermann reaction of blood +++++
167	F	Housewife	Vision falling for years; under care of Christian science practitioner; right cornea abraded; insensitive opacity of iris; left the same	R. Light perception L. Same	R. 16 L. 42%	R. Cataract L. Cataract with tension congestive glaucoma	11/15/27 iridotasis	11/28/27. Extraction of cataract; lens adherent to lens fossa, but got it anteriorly with iris forceps 11/28/27, 8:30 p. m., choroidal hemorrhage 11/29/27. Enucleation
165	M	Laborer	Vision falling for year; occasional pain along side of head; both pupils dilated; anterior chambers shallow; corneas stippled	R. 2/200 L. 1/200	R. 70 L. 70	Noncongestive	10/18/27 iridotasis, both eyes	12/16/27 R. 20 L. 23	2/28/27 R. 18% L. 18% 2/21/28 R. 42 L. 26	2/28/27 R. 4/200 L. Perception of light
170	F	None	Vision in left eye began falling in June, 1923; in September vision in left eye completely lost; vision in right eye began falling about the same time and was lost in April, 1927; anterior chamber fairly good; pupils dilated eccentrically; new vessels formed on iris; some postzygociliary; cornea hazy; arcus similarly marked; opacity of both lenses	No light perception in either eye	R. 80% L. 85%	Noncongestive	12/13/27 iridotasis, right eye 1/17/28 iridotasis, left eye	2/15/28 R. 40% L. 13%	3/15/28 R. 42 L. 26	Results not good Could not incise iris well owing to synechia; profuse hemorrhage; blood sugar from 400 to 380 mg.; after anterior chamber was emptied, tension did not go down

The details of the study are collected in table 2. Immediately below the averages of these details, we have tabulated the averages obtained in examinations of thirty-seven normal persons, for comparison. These thirty-seven were normal persons and persons with roentgenologic evidence of healed parenchymal tuberculosis (part 2).

In all the cases of this small series, we have established that there are definite vascular alterations, in the form of urinary changes, changes

TABLE 2.—The Results of Correlative Examinations of Fourteen Patients with Glaucoma;

Individual Number	Bilster Time, Hours	Permeability of Capillaries, %	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / O Ratio	Sugar, Mg.	Globulin, per Cent	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance (Electric)	Changes in Urine	Blood Pressure, Systolic	Blood Pressure, Diastolic	Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure X Pulse Rate, %	CO ₂ Combining Power
137	15	61	4	8.1	18.2	2.24	73	37	..	2	3.6	1.9	Trace of albumin	119	67	78	+ 7	+ 9	51.9
140	0	68	0	11.4	29.7	2.61	82	37	..	2½	0.45	Trace of albumin	100	70	68	+10	+10	55.6
141	9	28.2	3.13	86	2	0.2	Trace of albumin +	118	78	84	+ 9	0	61.6
145	15	66	4.4	10.1	15.7	1.55	70	55	+++	2¾	+19	0.35	Trace of albumin	136	80	84	+43	+43	55.4
148	15	56	3.7	9.7	24.3	2.50	79	24	..	1½	+17	0.26	116	74	90	+ 8	+18	60.3
150	15	57	3.7	12	21.3	1.78	82	15	..	1½	+39	0.32	Hyaline casts	140	86	84	+ 6	+ 6	62.7
153	15	78	5	9	18.7	2.08	83	0	..	1½	+ 2	0.15	Granular casts	124	58	64	+10	+10	62.2
154	15	60	4	23.08	71	3	..	1½	+18	0.09	? Hyaline casts	194	118	68	56.6
160	15	66	4.4	10.86	21.58	1.98	65	44	..	1½	+16	0.4	? Hyaline casts	128	64	68	+ 8	+28	62.7
161	5	72	14	9.17	18.03	1.96	86	23	..	1¼	16	1.4	Trace of albumin	107	64	88	+25	+51	49.4
164	9	71	8	8.7	16.54	1.80	65	20	+++	2¾	- 4.7	0.23	Granular casts	110	76	80	+14	+35	55.9
165	11	60	5.5	10	17.94	1.79	80	16	..	1½	+ 0.5	0.18	Hyaline casts	170	100	110	53.9
167	15	56	3.7	12	22.72	1.9	81	27	..	2	0.7	0.85	137	92	84	62	80	47.9
170	15	72	5	10.58*	23.71	2.2	320	36	+33	0.07	188	96	104	52.3
Averages*	13.3	64	4.8	10	21.4	2.14	77	25	2+	1½	+12.4	0.48	134	80	82	+18	+29	57.2
Averages†	7	63.3	9.4	10.1	20.6	2.04	71.3	30		2	+ 6.3	0.35	116	69	71	+16.5	+24	56

* For 14 patients with glaucoma.

† For 37 normal persons.

in the capillaries of the skin, increased blood pressure, sclerosis of the larger thoracic vessels, or a history of disease known to be associated with autonomic vascular disturbances (asthma, hay-fever).

The intracutaneous reactions may also be interpreted in this direction. Thus, the flare of the reaction to morphine is diminished, and the flare of the reaction to caffeine and that of the reaction to thyroxin are absent. The wheal in the reaction to epinephrine, on the other hand, is diminished. The wheal in the reaction to thyroxin is increased.

Comparison of the Averages of These Results with the Averages for Thirty-Seven Normal Persons

Endothelial Reaction (Rumpel-Leede)	Roentgen Examination of Chest		Capillaries of the Skin (Microscopic Examination)	Reaction to Ice, Seconds	Age	Weight / Length	Cholesterol, Mg.	Intracutaneous Reactions										X-Ray Diagnosis
	Heart	Tuberculosis						Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Morphine, Wheal, Mm.	Morphine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Caffein, Wheal, Mm.	Caffein, Flare, Mm.			
..	Asthenic	Dilatation	30	61	166	222	15.4	11	13.5	10	13	0	18	0			
..	Asthenic	+	40	45	...	158	18	8	11	10.7	27	0	30	0	Active tuberculosis of right upper lobe		
+	Sthenic	Granulation	15	48	...	267	17.4	7.7	9	7	10	13	23	0			
..	Sthenic	Granulation	20	71	166	208	18	13.6	16	0	16	0	23	0	Syphilitic aortitis		
..	Asthenic	Fibrosis	Granulation	10	67	182	317	18	12	9.7	0	17	0	18	0	Arteriosclerosis (aorta)		
..	Sthenic	Fibrosis	7	67	238	247	17	14	18.5	9.5	16	0	23	0	Pulmonary fibrosis		
..	Sthenic	Healed parenchymal	Diminished dilatation	30	75	223	175	22	6.5	9.5	0	18	0	22	0	Slight arteriosclerosis; fluid in chest		
..	Asthenic	Granulation	20	55	181	180	23	10	13.5	0	26	0	28	0	Arteriosclerosis (aorta)		
..	Sthenic	Healed parenchymal; fibrosis	Normal	10	58	181	190	16	8	12	0	20	0	24	0	Arteriosclerosis (aorta); bronchiectasis; emphysema		
..	Sthenic	Dilatation	12	43	171	208	14	13	5.5	10.7	13	0	20	0			
..	Sthenic	Healed parenchymal	15	49	223	185	18	14.7	17	12.5	(Not done)				Syphilitic aortitis		
..	Sthenic	5	52	250	185	17	13	10	13.7	25	0	31	0	Hypertrophy of heart; dilatation of aorta		
..	Asthenic	Dilatation	5	77	158	256	17	14.25	12	9	15	0	18	0	Scoliosis; bronchiectasis		
..	Sthenic	56	247	170	(Not done)									Arteriosclerosis (aorta); bronchiectasis	
..	15.6	58.7	199	212	17.7	11.2	12.1	6.4	18	1	23	0			
..	15.5	41.8	221	228	20	9	11.3	16.2	11.4	5.8	17.4	2.38			

VI. SENSITIZED PERSONS AND PERSONS WITH DISEASES OF THE SKIN

ANGIONEUROTIC EDEMA

CASE 152.—A white man, American, aged 27, had a swelling of the scrotum two years prior to the examination. The swelling lasted one day and returned at intervals of from three to four months for one year. During a remission, the patient received tetanus antitoxin. Four days later, his throat and tongue were involved. Two months later, the same kind of attack occurred. The last attack had lasted six days and was disappearing at the time of the examination.

The father had had angioneurotic edema for ten years. The mother once had urticaria. Two aunts had epilepsy. The patient had suffered at various times from attacks of migraine and was sensitive to strawberries.

This patient, it is to be noted, had a short blister time, with increased capillary permeability, a distinctly vagotonic reaction to epinephrine and diminished flares of the reactions to epinephrine and morphine with increased flares of the reactions to thyroxin and caffeine.

CASE 38.—A young Jewish druggist, aged 35, with a history of angioneurotic edema, had three sisters, one of whom had epilepsy, one of whom was nervous and one of whom was seemingly well. The father was 70 years of age and well. The mother was 65 years of age and suffered from neurasthenia. This patient formerly had a typical Sunday migraine. At the time of examination, he had pruritis, and was sensitive to raspberries. Formerly, ingestion of milk caused cramps and diarrhea. Watermelon still had this effect. At the time of examination, he was without angioneurotic manifestation.

As in the previous case, we find the patient in this case showing a short blister time with somewhat increased capillary permeability, but no chemical changes. The systolic reaction to epinephrine was vagotonic, but the pulse pressure showed an increase immediately after the injection. The capillaries of the skin appeared swollen and were markedly red, and in some a distinct granulation became apparent. The flares of the intracutaneous reactions (except of that to epinephrine) were all increased.

URTICARIA

CASE 171.—Menstrual Urticaria: A young woman, Jewish, aged 23, a laboratory worker, was alert, nervous and rather irritable. Her family history was negative except in relation to tuberculosis. The grandfather had had tuberculosis, and the mother died of tuberculosis. The patient had malaria in 1921. At the time of the examination, she had slight mitral insufficiency. She had had a rather irregular menstrual course. The urticaria, which was generalized, began one or two days before the menstrual period, and lasted approximately a week. The patient was then free from urticaria during the intermenstrual period. The patient recently had had a curettage and since then had been free from disturbance.

The comparison of the observations during the menstrual period with the intermenstrual observations is of interest. During the menstrual period, the permeability of the capillaries was increased, the potassium level, as well as the

K/Ca ratio, was lowered, there was less cholesterol and the systolic blood pressure and the pulse rate were higher. The reaction to epinephrine was sympathetictonic during both periods, more so during the intermenstrual time, when, too, the intracutaneous reaction to epinephrine was more marked. The wheals of the reactions to thyroxin and caffein were larger than normal at both times.

CASE 116.—A young Irish woman, aged 30, came to America four years prior to the examination. The first attack of urticaria appeared two years before the examination, when she had angioneurotic edema. Two months before, her father died of pernicious anemia and the attack in question dated from this time. The urticaria was worse at night and because of the interference with sleep the patient was rather nervous. The family history was negative. On general physical examination, the spleen was found enlarged, the icteric index was increased and bile was also present in the urine. With minor exceptions, the urticaria had persisted to the time of examination. No definite sensitization could be determined, but the skin was particularly sensitive to staphylococci. The function of the reticulo-endothelial system, as determined by administration of a vegetable oil (oleokinol), seemed practically normal.

The results of the examination were as follows: A strikingly short blister time, low permeability of the capillaries and a distinctly vagotonic reaction to epinephrine with the pulse pressure much increased. The results of all the chemical examinations were within the normal limits.

CASE 139.—A stenographer, American, aged 29, had vitiligo for ten years and urticaria for some eight weeks. She had jaundice at the age of 11, for two weeks. Of late, she had been nervous, with occasional palpitation. She had a nervous breakdown at the age of 19. She felt "shaky" when she worked hard, but had suffered no loss of weight. One other sister had vitiligo and one had diabetes. The urticaria was made worse by pineapple, popcorn and watermelon.

Practically the only abnormalities were that found in the pulse rate and the vagotonic reaction to epinephrine. There was a trace of albumin in the urine. The intracutaneous reactions to epinephrine and morphine showed lessened wheals and those to thyroxin and caffein increased wheals and flares. The patient was treated with calcium for two months. On reexamination, the blister time was somewhat shortened, the permeability of the capillaries was increased and the calcium was lower. During this time, however, the patient was somewhat improved.

ECZEMA

CASE 101.—A laborer, aged 55, born in Scotland, one of our group of 100 normal men, had chronic eczema of the legs. He had a history of moderate alcoholism. The family history was negative, except that one uncle had epilepsy. The patient was rather stolid and seemingly unemotional. Fifteen years prior to the examination, he had had rather severe diarrhea and with it urticaria.

The examination of this patient revealed merely a low capillary permeability together with a diminished intracutaneous reactivity to morphine. The reaction to epinephrine was sympathetictonic.

CASE 132.—The clinical history of the patient, the most interesting of the entire group of patients, has been described. It is to be recalled that he had the lowest K/Ca ratio of all the patients, the lowest CO₂ combining power and

increased muscle reactivity. The cholesterol level was high, the Kromayer light erythema faint, the pulse rate slow and the reaction to epinephrine vagotonic. The wheals of the reactions to thyroxin and caffein were somewhat increased.

The results of the examination of this patient emphasize the impossibility of schematizing the results and the futility of endeavoring to place these persons in hard and fast groups. The patient was typically vagotonic, but, in addition, he was suffering from a relative acidosis. Despite this acidosis, the muscular irritability was high.

GASTRO-INTESTINAL SENSITIZATION

CASE 54.—A man, American, aged 49, showed a trace of albumin in the urine and x-ray evidence of myocarditis and sclerosis. He was sensitive to peaches and strawberries (urticaria). The reaction to epinephrine (systolic) was distinctly vagotonic, but the pulse rate was sympatheticotonic.

CASE 172.—A Greek, aged 30, who had had a positive Wassermann reaction in 1921, had Raynaud's disease. The family history was negative. The calcium level was high (low K/Ca ratio), the reactions to the Kromayer light and ice were faint, the blood pressure was low and the reaction to epinephrine was markedly sympatheticotonic. All intracutaneous reactions to the pharmacologic substances injected were marked. The patient was sensitive to peaches and cherries.

CASE 169.—The patient had Buerger's disease (Wassermann reaction ++++). He showed a high calcium level with a low K/Ca ratio. The serum proteins were concentrated, the reaction to Kromayer light was faint and the reaction to epinephrine (systolic) was vagotonic. The flares of all the intracutaneous reactions (except that to epinephrine) were absent. The patient was sensitive to strawberries.

CASE 14.—A German, aged 36, an artisan, had albumin and casts in the urine, together with an undetermined reducing substance (not dextrose). He probably had gallbladder disease. He was sensitive to honey and pineapple; these caused intense pain. The capillaries of the skin were increased in number, and their permeability was high. The calcium level was high and the K/Ca ratio was low. The cholesterol level was also high and the reactions to the Kromayer light and ice were faint. The reaction to epinephrine was vagotonic. The wheal of the reaction to epinephrine was increased and the flare diminished.

PURPURA

CASE 120.—A Hungarian woman, who gave a history of sensitiveness to tomatoes, on admission had petechial hemorrhages over the body and the extremities, showers appearing at intervals of from twenty-four to forty-eight hours. There was considerable blood in the urine. It may be noticed that the permeability of the capillaries was high and the endothelial reaction (Rumpel-Leede) was positive. The blood chemistry was normal, except for an increase in the globulins. Microscopic examination revealed distinct granulations of the skin capillaries.

PREVIOUS SENSITIZATION—HAY-FEVER

CASE 128.—An American workman, of Irish parentage, aged 66, stated that he had had hay-fever for years. In addition, he had an enlarged prostate and

x-ray evidence of arteriosclerosis of the larger vessels. The capillaries of the skin showed distinct granulations and the urine contained albumin. The blood chemistry was practically normal.

CASE 148.—A white woman, aged 67, had glaucoma and vitiligo. She had had hay-fever twenty-five years prior to the examination and had had urticaria. X-ray examination of the chest showed considerable healed pulmonary tuberculosis and arteriosclerosis, and she gave a history of having had cerebral hemorrhages. The capillaries of the skin showed granulations; the reaction to epinephrine was vagotonic.

CASE 140.—A white man, aged 45, suffering from alcoholism and glaucoma, had a history of hay-fever every spring. There was roentgenologic evidence of active tuberculosis. Examination of the capillaries of the skin showed dilatations, but the total number was diminished. There was a trace of albumin in the urine and the reaction to epinephrine was vagotonic.

CASE 93.—An American workman, aged 53, a periodic drinker, had a history of hay-fever every fall (ragweed). In addition, he was sensitive to halibut. He was short of breath and the x-ray picture indicated a myocarditis. The reaction to epinephrine was vagotonic; the capillaries appeared to be normal.

CASE 160.—A white man, American, aged 58, was suffering from glaucoma. He gave a history of asthma extending over many years. An x-ray picture of the chest indicated emphysema and bronchiectasis, together with arteriosclerosis of the larger vessels. The reaction to epinephrine was vagotonic. The capillaries appeared to be unchanged.

CASE 36.—A white man, American, aged 43, had an attack of hay-fever four or five years prior to the examination. The reaction to epinephrine was vagotonic, and there was a trace of albumin in the urine.

All the members of this group showed relatively high K/Ca ratios, CO₂ combining power within normal limits and faint reactions to the Kromayer light. Their blood pressures were relatively low and their pulse rates were somewhat increased.

PREVIOUS SENSITIZATION—URTICARIA AND ANGIONEUROTIC EDEMA

CASE 45.—An American workman, aged 39, had a history of scarlet fever with involvement of the kidneys at the age of 4. The blood pressure was 162 systolic and 114 diastolic. The reaction to epinephrine was vagotonic. The patient had had urticaria twenty years before.

CASE 86.—A former dentist, aged 50, was extremely nervous, with a history of alcoholism. He had had angioneurotic edema twenty-five years before. The reaction to epinephrine was vagotonic.

CASE 56.—An American workman, aged 44, had x-ray evidence of active pulmonary tuberculosis. He had had angioneurotic edema and dermatographia three years before. The reaction to epinephrine was vagotonic.

CASE 77.—An American workman, aged 39, formerly suffered from alcoholism. His grandfather had asthma. He stated that he had had sugar in the urine and that ten years ago he had urticaria from eating sweet potatoes. The patient was

nervous. He gave a vagotonic reaction to epinephrine and a positive endothelial reaction (Rumpel-Leede).

CASE 80.—An American workman, aged 29, was nervous and had a distinct tremor. He had had urticaria three years before. He gave a distinct vagotonic reaction to epinephrine.

The Results of Correlation

Patient	Diagnosis	Blister Time, Hours	Capillary Permeability, %	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Sugar, Mg.	Protein, Mg.	Globulin, Mg.	CO ₂ Combining Power	Cholesterol, Mg.	Kromayer Light Erythema Time, Min.	Skin Resistance	Ice Reaction	Basal Metabolic Rate	Blood Pressure		Pulse Rate	Reaction to Epinephrine	
																	Systolic	Diastolic		Pulse Pressure, %	Systolic
152	Angioneurotic edema	4	73	18	9.8	20.1	2.05	63	7.47	20	63.4	175	60	0.18	15	4.8	129	74	80	-5	Vagotonic
38	Angioneurotic edema	5	69	14	9.8	21	2.14	86	8.28	40	58.5	...	90	0.29	10	11.5	124	65	84	+31	Vagotonic
171	Menstrual urticaria	5	73	14	12.6	17.9	1.42	72	48.7	202	75	0.08	20	8	114	66	96	+18	Sympatheticotonic
	(Intermenstrual observations)	6	64	10	12.6	21.3	1.68	64	7.41	...	46	230	...	0.08	..	12	102	68	65	+100	Sympatheticotonic
116	Urticaria	3½	60	17	10	19.4	1.94	78	6.98	40	55.1	175	30	0.60	20	9	128	50	80	-17	Vagotonic
139	Urticaria and vitiligo	6	65	11	9.7	18.4	1.9	81	7.10	18	50	175	120	0.20	8	5	113	71	104	+12	Vagotonic
101*	Eczema	4½	68.5	15	8.6	18.7	2.1	78	7.95	...	50	190	132	76	67	+13	Sympatheticotonic
		8¾	47	5.4	9.4	19.4	2.06	65	7.20	45	57.4	158	90	0.13	15	31	132	76	67	+13	Sympatheticotonic
132	Eczema	6	68	11.3	13.4	15	1.12	67	7.30	23	40.3	256	120	0.31	10	-1.2	132	78	56	0	Vagotonic
54*	Sensitized	6	60	10	...	22	...	80	8.28	33	56.6	...	75	0.26	25	-3.4	108	68	72	+90	Vagotonic
172	Sensitized	12	72	6	13	21.3	1.64	76	8.16	165	0.08	45	-16	108	78	94	+90	Sympatheticotonic
169	Sensitized	15	62	4.1	12.3	19.24	1.56	67	9.87	20	55.1	158	120	0.23	25	-7	118	78	82	+40	Vagotonic
14*	Sensitized	7	74	10.5	11.2	19.6	1.75	67	8.06	37	65	278	95	0.20	40	2.7	128	80	76	0	Vagotonic
120	Purpura	6	82	13	10	19.9	1.99	71	7.95	50	52.2	185	70	...	14	-5
128*	Hay-fever for years	15	68	3.8	10.2	19.7	1.93	79	8.06	55	58.1	230	240	1	24	-18	122	70	84	+24	Vagotonic
148	Glaucoma	15	56	3.7	9.7	24.3	2.5	79	7.97	24	69.5	317	85	0.26	10	+17	114	72	94	+18	Vagotonic
140	Glaucoma	15	68	4.05	11.4	29.7	2.61	82	6.25	37.5	55.6	158	150	0.45	40	...	100	70	70	+10	Vagotonic
93*	6	50	8.3	7.6	24.5	3.22	70	8.59	42	57	230	90	0.25	12	0	113	71	86	+19	Vagotonic
160	Glaucoma	15	66	4.4	10.86	21.58	1.98	65	8.16	44	62.7	190	70	0.4	10	+16	128	64	68	-28	Vagotonic
36*	Cardiovascular renal disease	8	58	7.2	12.1	26.3	2.17	90	8.28	33	57.6	...	120	0.11	20	+1.3	104	50	84	+28	Vagotonic
45*	Cardiovascular renal disease	6	54	9	11.2	16.6	1.48	77	7.73	40	54.3	...	45	0.28	20	+20	162	114	84	+8	Vagotonic
86*	Nervous	15	58	3.8	12.6	15.9	1.26	94	6.33	40	55	185	105	0.36	25	+6.4	118	60	74	-14	Vagotonic
56*	(Roentgen evidence) tuberculosis	6	61	10	9.8	28.6	2.92	65	9.36	35	56.6	...	135	0.32	15	-17.9	124	88	80	+22	Vagotonic
77*	Nervous	9	87	10	10.8	15.6	1.44	71	6.98	36	60.6	196	240	1	35	+7.9	126	78	82	+7	Vagotonic
80*	Nervous	6	91	15.1	8	13.7	1.7	69	8.28	33	53.2	222	100	1.6	30	+13	116	68	64	+12	Vagotonic

* The patient belonged to the group of 100 so-called "normal" men.

COMMENT

When considering the results of the examination of the group of persons who were presumably sensitized, it must be kept in mind that one can hardly expect distinct chemical alterations in conditions in which the clinical manifestations were so frequently evanescent and transitory,

Nathan and Stern¹ rightly emphasized that a single determination of the K/Ca ratio—for instance, during the course of a dermatosis—hardly gives a true picture, typical for the disease. One must make repeated determinations in order to obtain a true insight into the fluctua-

Examinations of Sensitized Persons

Changes in Capillaries	Arteriosclerosis, X-Ray	Healed Tuberculosis	Active Tuberculosis	Intracutaneous Reactions								Endothelial Reaction	Age	Sex	Associated Conditions and History	
				Changes in Urine	Epinephrine		Morphine		Thyroxin		Caffein					
					Wheal, Mm.	Flare, Mm.	Wheal, Mm.	Flare, Mm.	Wheal, Mm.	Flare, Mm.	Wheal, Mm.					Flare, Mm.
.....	Hyaline casts	26	7.5	9.5	10	9	8	9	10	..	27	M	
Dilatations, granulations	18	8.6	8.8	25.4	10.2	10.4	4.8	11.6	..	39	M	
Dilatations	..	+	..	Albumin, faint trace	17.5	10.5	12.5	0	18	0	20	0	..	23	F	
Dilatations	..	+	26	6.5	10	12.2	20	0	17	8	..	23	F	
.....	Bile	20.4	7.4	9.2	8	5	0	18.2	0	..	30	F	
Dilatations	Albumin, faint trace	16	11	9.5	7.5	14	12.5	14	12	..	29	F	
Dilatations	..	+	19.6	7	10.2	6	10	0	18.4	0	+	55	M	
Dilatations	..	+	18.4	9.4	14.6	17.6	13.4	5	22.6	6	..	26	M	
.....	Albumin, trace	21.2	10.4	11	18	12	0	11	0	..	49	M	Sensitization to peaches and strawberries; cirrhosis probable
Dilatations	..	+	22.4	16	15.5	8.5	18	16	20	7.5	..	30	M	Raynaud's disease; syphilis, 1921; sensitization to peaches and cherries
Retina pale	..	+	20.8	11	13	0	18	0	21	0	..	27	M	Buerger's disease; syphilis (Wassermann +); sensitization to strawberries
.....	Casts	24.4	6.2	13.2	7.2	15	5	9.8	10	..	36	M	Probably gallbladder disease; intense pain caused by honey and pineapple
Granulations	Blood	21.2	7.2	9.6	8.2	12.1	0	13	0	+	18	F	Purpura hemorrhagica; sensitization to tomatoes
Granulations	+	+	..	Albumin	12.6	10.2	14.4	0	22.6	0	-	60	M	Hay-fever for years
Granulations	+	18	12	8.75	0	17	0	18	0	-	67	F	Hay-fever 35 years ago; cerebral hemorrhage; urticaria
Dilatations	+	Albumin	18	8	11	10.7	27	0	30	0	-	45	M	Hay-fever every spring; alcoholism
.....	20.4	8.6	12.4	15	10	0	22.4	0	+	52	M	Hay-fever every fall; sensitization to halibut; myocarditis; formerly dipsomania
.....	16	8	11	0	20	0	24	0	-	58	M	Asthma; emphysema
.....	Albumin	20.8	14.2	11.2	18	7.4	0	7.4	0	-	43	M	Slight attack of hay-fever 45 years ago
.....	20.4	9.8	14.2	21.4	16.4	12	20	4.8	-	39	M	Scarlet fever with kidney involvement at 4; urticaria 20 years ago
.....	18.8	14	11.8	19.6	15.4	12.4	22.2	0	-	50	M	Angioneurotic edema when a dental student 20 years ago; alcoholism
.....	17.2	5.8	10.8	22.4	13.4	7	21.4	7	-	44	M	Angioneurotic edema 3 years ago; dermatographia
.....	14	10.8	12.6	25	10	15.4	17	12.4	-	39	M	Grandfather had asthma; drug addict (?); urticaria 10 years ago; sensitization to sweet potatoes
Granulations	14.8	12.4	12.4	19.2	13.4	9.2	16.2	7	-	29	M	Sugar in urine formerly; alcoholism; urticaria in 1922; tremor

tions that are constantly taking place. We have emphasized this point of view in our study of the lymph changes during shock, etc.²

1. Nathan, E., and Stern, F.: *Klin. Wchnschr.* 7:1375, 1928.

2. Petersen, W. F.; Milles, Geo., and Müller, E. F.: *Ztschr. f. Exper. Path. und Therap.* 60:336, 1928; Petersen, W. F.; Müller, E. F., and Boikan, W.: *J. Inf. Dis.* 41:405, 1927.

The angioneurotic edemas and the urticarias studied seemed to be characterized by a short blister time and a relatively high inflammatory index. During an attack, the K/Ca ratio appeared to be lower. In general, the sugar level was higher. The menstrual urticaria was associated with a relative acidosis, and the reaction to epinephrine, in contradistinction to the reaction in other cases, was sympatheticotonic. Changes in the capillaries of the skin and changes in the urine were, of course, commonly associated. The intracutaneous reactions to the pharmacologic substances injected were not characteristic.

The small group of persons with gastro-intestinal sensitization all had high calcium levels and low K/Ca ratios. In two, however, distinct vascular diseases (Raynaud's and Buerger's) were associated.

Of the six persons with a history of hay-fever, three had glaucoma. Here the blood chemistry was changed so far as the K/Ca ratio was high. All were distinctly vagotonic and the capillary permeability was low in each case.

On the other hand, the persons with a history of previous angioneurotic edema and urticaria seemed to be of a somewhat different type. They were distinctly nervous and had low K/Ca ratios, but were, nevertheless, distinctly vagotonic. With two exceptions, both highly nervous persons, all showed low permeability. These two patients (nos. 77 and 80) had high resistance of the skin to electric current, high permeability of the capillaries and lessened thyroxin wheals.

The endothelial reaction of Rumpel-Leede did not seem to be characteristic for the groups.

VII. A STUDY OF EIGHTY-THREE TUBERCULOUS PATIENTS

A. GENERAL CORRELATIONS

The study of resistance to tuberculous infection, conditioned by innumerable biologic interactions, seemingly offers insurmountable difficulties. The cellular factors, the still intangible effect of sensitization, intercellular and intracellular digestion, humoral and fixed antibodies, endocrine, vitamin, and chemical equilibriums must be considered. Add to these chance pathologic complications, constitutional inequalities, peripheral and visceral autonomic vascular and metabolic responses and emotional factors, as well as environmental influences, and one begins to shuffle some of the cards of the intricate game—all this, of course, without considering differences in the virus itself.

The organism has but two means at its disposal in overcoming the clinical disease: resorption, i.e., digestion, and its antithesis, encapsulation or insulation. Early in the disease, the former method is probably frequently successful; even in well advanced diseases, it probably plays a rôle of greater importance than is usually believed, especially in peripheral tuberculosis. But from the practical clinical standpoint, it appears that the inhibition of digestion, the suppression of inflammatory response, is of greater importance for the welfare of the patient with pulmonary tuberculosis.

Hippocratic medicine was clearly cognizant of the seasonal influence on the mortality from tuberculosis. General biologic activation in the spring, incident to environmental and intrinsic changes, is followed by dissemination of the virus. It is a condition that cannot be explained on any anatomicopathologic basis. Not only is the virus disseminated; the endothelium and other tissues of the body are receptive. This factor, as well as the analogous effect of the menstrual cycle, we discussed previously at some length.¹ Here, too, we pointed out the possible significance of changes in the status of the capillary endothelium.

In the analysis of the results of the examinations of the group of 100 so-called "normal" men (part II), we pointed out that nine gave roentgenologic evidence of active parenchymal lesions. The persons examined were workingmen; in the majority, the lesions did not present sufficient clinical manifestations to make the men aware of an unusual pulmonary disturbance. In the analysis, however, we found that this group did show a number of deviations from the "normal" (prolonged

1. Levinson, S. A., and Petersen, W. F.: *Am. Rev. Tuberc.* **15**:681, 1927.

TABLE 1.—Index of the Tuberculous Patients Examined

Patient	Age	Nationality	Advance Diagnosis;* Pulse Rate	Tem- perature	Result of Roentgen Exami- nation for Tuber- culosis	Dura- tion of Activ- ity, Weeks	Condi- tion on Exami- nation; Weight †	Condition at Time of Writing ‡	Outcome
1	27	Jewish	M.A. A.	72-78 98.2-98.4	Positive, not active	156	M.A. A. →	M.A. A. G. →	Discharged, living, improved
2	22	Jewish	Min. B.	60-76 97-98.4	R. apical healed pa- renchymal	20	Min. B. →	Min. B. G. →	Discharged, living, condition quiescent
3	21	Polish	Min. A.	72-96 96.2-98.6	Negative	6	Min. →	Min. A. G. → colloid goiter	Sanitarium
4	30	American	Min. A.	68-72 97-98.2	Negative	208	Min. →	Min. A. G. →	Discharged, living, improved
5	20	Swedish	M.A. B.	104-120 98-98.8	M.A.*	60	M.A. B. ↑	M.A. B. F. →	Sanitarium
6	27	German- American	Min. A.	66-84 97-99.4	Apical	200	Min. A. ↑	Min. A. G. ↑	Sanitarium
7	54	Norwegian	F.A. B.	72-94 96.5-99.2	F.A.*	28	M.A. B. ↓	F.A. B. P. ↓ tuberculosis of larynx	Discharged, died
8	35	Mexican	Min. A.	76-90 97-98.6	Negative	20	Min. ↑	Min. A. G. ↑	Discharged, living, condition arrested
9	43	Polish	M.A. A.	80-92 97.2-99	F.A.	94	M.A. A. →	M.A. A. P. → dry pleurisy and arthritis	Died
10	27	American	Min. A.	80-92 96-98.2	Negative	350	Min. →	Min. A. G. →	Discharged, living, improved
11	42	American	Min. A.	72-80 97.6-98.6	Negative	22	Min. A. →	Min. A. G. →	Discharged, living, improved
12	37	German	M.A. A.	84-88 97.8-99.4	F.A.	208	M.A. A. →	F.A. A. P. → cyst adenoma of thyroid, tuber- culous colitis	Died, April, 1929
13	23	American	Min. B.	70-82 97-98.4	Negative	28	Min. B. →	Min. B. G. →	Discharged, living, improved
14	17	American	Min. B.	72-84 97.8-98.6	Tubercu- losis of hilum	16	Min. B. ↑	Min. B. G. ↑	Discharged, living, improved
15	40	Norwegian	F.A. A.	80-92 96-98.6	F.A.	200	F.A. A. →	F.A. A. P. → tuberculous laryngitis and enteritis	Discharged, living, not improved
16	25	Polish	Min. A.	78-90 97-98	Tubercu- losis of hilum	572	Min. A. ↑	Min. A. G. ↑ tuberculous colitis	Discharged, living, condition arrested
17	40	German	Min. A.	76-80 97.8-98.6	Negative	17	Min. A. →	Min. A. G. →	Discharged, living, condition quiescent
18	36	Swedish	F.A. B.	100-115 97-102.4	Positive	200	F.A. A. ↓	F.A. A. P. ↓ Wassermann 4 plus; cavities in lung; artificial pneumothorax; spon- taneous hemorrhages from lung	Died
19	54	Irish	F.A. B.	84-88 97.4-98.6	Positive	290	F.A. A. →	F.A. A. G. → Wassermann 3 plus; syphilitic aortitis	Sanitarium
21	32	Norwegian- American	Min. A.	78-100 97-98.8	Positive	28	Min. A. ↑	Min. A. G. ↑	Discharged, living, condition quiescent

* In diagnosis of tuberculosis, M.A. means moderate advanced at time of examination; Min., minimal or incipient, and F.A., far advanced; A., B. and C. added to these designations denote degrees of activity.

† → means weight stationary at time of examination; ↑, weight increasing; ↓, weight decreasing.

‡ In this column, G. means good prognosis at time of examination; F., fair prognosis, and P., poor prognosis.

TABLE 1.—Index of the Tuberculous Patients Examined—Continued

Patient	Age	Nationality	Advance Diagnosis; Pulse Tem- perature	Result of Roentgen Exami- nation for Tub- erculosis	Dura- tion of Acti- vity, Weeks	Condi- tion on Exami- nation; Weight	Condition at Time of Writing	Outcome
22	44	Dutch	M.A. A. 80-90 98.6-98.8	F.A.	130	M.A. A. ↓	F.A. A. G. → fibroid	Sanitarium
23	22	Polish	F.A. A. 74-80 98.6-98.6	Positive	191	F.A. A. →	F.A. A. P. →	Sanitarium
24	37	Austrian	M.A. A. 76-84 97-98	Positive	30	M.A. B. ↑	Min. A. G. →	Discharged, living, improved
25	25	Polish	F.A. A. 86-88 97-98.8	Positive	114	F.A. A. ↓	F.A. C. P. ↓ Spontaneous collapse	Died
26	24	American	M.A. A. 72-80 98-98.6	Positive; cavity in right apex	156	M.A. B. →	F.A. A. P. → Tuberculous enteritis	Died, March, 1929
27	43	German- American	M.A. A. 78-90 98.4-98.6	F.A.	104	M.A. A. ↑	M.A. A. G. ↑ fibroid	Sanitarium
28	42	Bohemian	F.A. B. 72-102 97.8-101.3	F.A.	312	F.A. A. →	F.A. C. P. ↓ tuberculous enteritis and meningitis	Died
29	31	American	Min. A. 72-90 98-98.6	Positive	213	Min. A. →	Min. A. G. →	Discharged, living, condition arrested
30	20	Italian	M.A. A. 94-100 97-99	Positive	104	M.A. A. →	M.A. A. G. →	Discharged, living, condition quiescent
31	21	Austrian	Min. B. 68-72	Positive	230	Min. B. →	M.A. A. P. →	Sanitarium
32	27	Irish	F.A. A. 72-86 97-98.6	In apex	26	F.A. A. →	F.A. A. P. →	Discharged, living, condition arrested
33	29	Finnish	M.A. B. 90-100 98.2-98.6	F.A.	780	M.A. B. ↓	M.A. B. G. →	Discharged, living, condition quiescent
34	25	American	F.A. B. 72-88 97.4-98.8	F.A.	104	F.A. B. →	F.A. B. P. ↓ Wassermann 4+; dermatitis exfolia- tiva; cavities in lungs	Discharged, died
35	40	Polish	Min. B. 70-90 97.4-98.6	Negative	29	Min. B. →	Min. B. G. →	Discharged, living, condition quiescent
36	42	Polish	F.A. A. 80-98 94-100.4	F.A.	312	F.A. A. ↓	F.A. A. F. ↓	Died, November, 1928
37	17	Jewish	Min. A. 80-84 97.2-98	Negative	828	M.A. →	Min. A. G. →	Discharged, living, condition quiescent
38	42	Norwegian	F.A. B. 74-92 98-98.6	F.A.	276	F.A. B. →	F.A. A. P. →	Discharged, living, condition arrested
39	45	American	M.A. B. 72-90 97-98.6	F.A.	156	M.A. B. ↑	M.A. B. F. ↑	Sanitarium
40	26	Bohemian	F.A. B. 74-96 97.8-98.6	M. A.	260	F.A. B. →	F.A. B. P. →	Discharged, living, condition quiescent
41	20	Jewish	F.A. B. 78-100 97.4-98.8	F.A.	78	F.A. B. →	F.A. B. P. →	Discharged, living, improved
42	29	German	F.A. B. 78-84 97.2-98.4	F.A.	156	F.A. B. →	F.A. B. P. → tuberculous laryngitis	Sanitarium
43	29	American	M.A. B. 80-86 97-98.6	Positive; fluid	52	F.A. A. ↑	M.A. A. G. ↑ pleurisy; fluid	Sanitarium
44	31	Swedish	M.A. A. 74-106 98-99.8	Positive; fluid	44	F.A. A. ↑	F.A. A. F. ↑ fluid	Discharged, living, condition arrested

TABLE 1.—Index of the Tuberculous Patients Examined—Continued

Patient	Age	Nationality	Advance Diagnosis; Pulse Tem- Rate perature	Result of Roentgen Exami- nation for Tuber- culosis	Duration of Activ- ity, Weeks	Condi- tion on Exami- nation; Weight	Condition at Time of Writing	Outcome
45	34	American	F.A. B. 86-110 97 -100	F.A.	104	F.A. A. ↑	F.A. A. F. ↑	Discharged, died
46	24	German	F.A. B. 92-100 98.4-98.8	F.A.	130	F.A. B. ↑	F.A. A. G. ↑	Sanitarium; improved
47	21	Polish	F.A. B. 100-120 98.8-100.4	F.A.	156	F.A. A. →	F.A. A. P. ↓	Died
48	21	Lithuanian	F.A. A. 80- 88 98.4-98.6	F.A.	270	F.A. B. ↓	F.A. C. P. ↓ cavities in lungs; tuberculous laryn- gitis and enteritis	Died
49	38	German	M.A. B. 72- 98 98.2-100	F.A.	70	M.A. B. ↑	M.A. B. P. → tuberculous enteritis	Discharged, died
50	21	Polish	Min. B. 76- 80 97.2-98.6	Positive	70	Min. A. ↑	M.A. A. G. →	Sanitarium
51	30	Danish	M.A. B. 80- 92 97.4-98.8	F.A.	64	M.A. B. ↓	F.A. B. F. ↑ pneumothorax; thoracoplasty	Sanitarium; stationary
52	19	American	F.A. B. 76-104 98.4-99.8	Positive; fluid	52	F.A. B. ↑	M.A. A. F. ↑ serofibrinous pleuritis; tuber- culous enteritis	Discharged, living, improved
53	20	German	M.A. B. 86-120 97.4-99.8	Positive	38	M.A. B. →	M.A. B. P. ↓	Discharged, living, not improved
54	20	German	M.A. B. 76- 94 97 -99	Positive	104	M.A. B. ↑	M.A. A. F. ↑	Discharged, living, improved
55	21	Swedish	M.A. A. 68- 86 97.6-98.6	Positive; fluid	104	M.A. B. ↑	M.A. B. F. ↑ fluid	Sanitarium
56	26	Swedish	M.A. A. 78- 88 98 -98.6	Positive	208	M.A. A. ↑	F.A. A. F. →	Sanitarium
57	22	Irish	M.A. A. 62- 82 97 -98.2	M.A.	208	M.A. ↑	M.A. G. ↑ pleurisy; arthritis	Discharged, living, improved
58	28	American	F.A. B. 80-100 97 -100.8	Positive	208	F.A. B. ↑	F.A. B. P. →	Sanitarium
59	20	Austrian	F.A. B. 80- 90 98.2-98.8	Positive	156	F.A. B. →	F.A. B. P. → pleurisy	Sanitarium; fair condition
60	26	Swedish- Norwegian	M.A. A. 88- 99 97 -98.6	F.A.	108	F.A. C. ↓	F.A. C. P. ↓ cavities in lung; enteritis; colitis	Died
61	25	American	F.A. C. 84- 96 98 -99.8	F.A.; emphysema	200	F.A. C. ↓	F.A. C. P. ↓ artificial pneumo- thorax; renal tuberculosis	Discharged, died
62	49	Irish	F.A. A. 70- 84 97.6-98.8	Old tuber- culosis; fluid	312	F.A. A. →	F.A. A. F. → old tuberculosis with fluid; artifi- cial pneumo- thorax in 1926	Sanitarium; well
63	25	Bohemian	F.A. A. 90-100 98 -98.6	F.A.	104	F.A. C. ↑	F.A. C. P. ↓ phrenicotomy; thoracoplasty	Sanitarium
64	31	Swedish- English	F.A. B. 80- 84 97.6-98.6	F.A.	104	F.A. B. ↑	F.A. B. P. ↓ multiple cavities in lung	Died, March, 1929

TABLE 1.—Index of the Tuberculous Patients Examined—Continued

Patient	Age	Nationality	Advance Diagnosis; Pulse Rate	Tem- perature	Result of Roentgen Exami- nation for Tuber- culosis	Dura- tion of Acti- vity, Weeks	Condi- tion on Exami- nation; Weight	Condition at Time of Writing	Outcome
65	52	German	M.A. B. 92-98	97 -97.5	Old tuber- culosis	31	M.A. A. →	M.A. A. G. →	Discharged, living, condition quiescent
66	45	Swedish	F.A. B. 88-108	96 -100	F.A.	150	F.A. B. ↓	F.A. C. P. ↓	Died
67	23	Swedish	F.A. B. 78-102	98.6-100.6	F.A.	60	F.A. B. ↑	F.A. C. P. ↓	Sanitarium; active
68	20	American	M.A. A. 92-138	98.6-103.4	F.A.	64	M.A. A. ↑	F.A. B. P. ↓	Died
69	34	German	F.A. B. 80-100	98.4-99.2	F.A.	208	F.A. B. ↑	F.A. C. P. → tuberculous laryngitis	Died
70	45	Polish	F.A. B. 82-90	98.4-99	F.A.	408	F.A. B. →	F.A. B. F. → dry pleurisy	Died, December, 1928
71	41	American	M.A. B. 80-82	98 -98.4	F.A.	156	M.A. B. ↑	F.A. A. F. ↑	Sanitarium
72	26	Irish	Min. B. 72-88	97 -99	Of hilum	89	Min. B. ↑	Min. B. G. ↑	Discharged, living, condition arrested
73	43	American	M.A. B. 94-88	97.8-99	F.A.	26	M.A. B. ↑	M.A. A. F. ↑ diabetes	Discharged, living, improved
74	45	Swedish	M.A. A. 88-108	97.2-98.6	F.A.	150	F.A. B. ↓	F.A. B. P. ↓ diabetes	Died
75	33	American	M.A. B. 92-116	97.8-100.2	F.A.	55	F.A. A. →	F.A. A. F. →	Died, living, im- proved
76	38	American	F.A. B. 92-122	98.4-100.4	F.A.	52	F.A. B. ↑	F.A. A. F. ↑	Died, living, con- dition quiescent
77	41	American	M.A. B. 67-94	96.6-98.8	Positive	180	F.A. B. →	F.A. B. F. →	Died
78	27	Japanese	M.A. B. 88-120	99 -98.8	Positive; fluid	40	M.A. B. ↓	F.A. B. P. ↓ serofibrinous pleuritis	Discharged, died
79	17	American	M.A. A. 76-92	97.2-98.9	M.A.	100	M.A. A. ↑	M.A. A. F. ↑	Sanitarium
80	35	American	Min. B. 68-86	97.8-98.2	Old tuber- culosis	52	Min. B. ↑	M.A. A. G. ↑	Discharged, living, condition arrested
81	25	American	F.A. B. 78-84	97.4-99	Positive	156	F.A. A. ↓	F.A. A. F. ↓	Discharged, liv- ing, improved(?)
82	37	German	M.A. B. 80-90	97.8-98.6	Positive	156	F.A. A. ↑	M.A. A. G. ↑	Sanitarium; condition quiescent
83	30	Slavic	M.A. B. 80-92	97.8-99.8	F.A.	130	F.A. B. ↑	F.A. B. P. ↓	Died

blister time, decreased permeability, lowered inflammatory index, abnormal K/Ca ratio, increased globulin, increased basal metabolic rate, diminished resistance of the skin to electric current, increased muscular irritability, increased pulse rate and blood pressure, delayed reaction to ice, etc.). The members of the group were considerably older than the average and some of the changes must be ascribed to age.

Nevertheless, we deal here with a tuberculous group apparently having a chronic form of the disease with little constitutional disturbance. We must assume that these persons are relatively resistant. Certain definite deviations (chemical, vascular, nervous, etc.) appear to be associated with this status.

One of the factors is a reduction of the inflammatory response. This diminishes, in general, with progressing age, but seems accentuated in the tuberculous group. For fifty persons with an average age of 58, the inflammatory index averages 8. Our group of nine with an average age

TABLE 2.—*A Summary of the Results of the Examinations of*

Clinical Classification of Tuberculosis	Cases	Sputum, per Cent Positive	Wassermann Reaction, per Cent Positive	Tuberculosis Fixation, per Cent Positive	Darby Reaction, per Cent Positive	Capillary Permeability Ratio	Blister Time, Hours	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Sugar, Mg. per 100 Cc.	CO ₂ Combining Power	Cholesterol, Mg. per 100 Cc.	Leucithin, Mg. per 100 Cc.
Incipient A.....	12	0	0	16	25	63	8.6	7.6	9.1	20.8	12.27	99	53.2	186	18
Incipient B.....	7	0	0	0	43	60	7	10	10.7	18.5	1.73	77	56.4	190	17.4
Moderately active A	13	30	0	46	61	70	8.4	8.8	10.8	17.1	1.6	86	58.7	211	16.5
Moderately active B	12	50	0	58	83	67	7.4	10.4	10.2	19.6	1.92	86	59.3	192	15.6
Far advanced A...	16	69	6	87	81	70	7.2	9.9	9.8	19	1.93	83	54.5	186	15.9
Far advanced B...	18	82	11	72	72	62	6.4	9.6	10.5	19.8	1.87	82	55.1	207	15.3
Far advanced C...	5	80	0	60	100	77	11.2	6.8	10.5	18.4	1.75	82	50	192	16.9

TABLE 3.—*A Comparative Summary of the Results of the Examinations of Tuberculous*

Type of Patients in Group	Cases in Group	Blister Time, Hours	Capillary Permeability, per Cent	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Sugar, Mg. per 100 Cc.	Globulin, per Cent	Serum Protein, per Cent	Kromayer Light Extinction Time, Min.	Basal Metabolic Rate,	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Rate
Group of 100 "Normal" Men																	
Actually normal.	20	6.7	63	9.4	10.2	20.6	2.05	71	33	8.04	130	+7.5	0.37	3.2	115	68	66
Showing healed parenchymal tuberculosis.....	12	7.3	65	9	10.3	20.3	1.97	73	24	7.86	120	+7	0.32	3.6	115	68	76
Showing active parenchymal tuberculosis, roentgenologically....	9	8.4	50	7	9.6	20.1	2.08	70	41.7	8.06	114	+18.2	0.28	2.2	133	73	78
Group of Patients in Sanitarium																	
Gaining weight...	36	7.2	65.3	9.5	10.6	18.9	1.80	85	33	8.73	90	+7.4	121	73	80
Stationary.....	32	7.6	66.2	8.6	10.4	20.1	1.96	84.7	37	8.55	91	+8	121	70	88
Losing weight....	13	7.7	60.6	9.7	10.2	17.7	1.73	86.6	43	9.03	79	+8.4	112	72	91

of 58.7 has an index of 7.5. The slowing of the reaction to ice is in line with the expectancy from the age of the group (column 19, table 1, part I.).

The diminution of the inflammatory response has taken place despite an increase in the basal metabolic rate, and the weight length ratio gives evidence that no serious inroad has been made so far as the general well being of the group is concerned.

Apart from the definite increase in the basal metabolic rate, the increase in globulins, the definite disturbance of the K/Ca ratio, the increase in the pulse rate, etc., offer evidence of the activity of the disease.

Tuberculous Persons Correlated on the Basis of Clinical Classifications

Corpuscles/Plasma Ratio	Kromayer Light Erythema Time, Min.	Complexion	Endothelial Reaction, per Cent Positive	Reaction to Ice, Seconds	Capillaries, per Cent Pathologic	Basal Metabolic Rate	Urine, per Cent Pathologic	Influenza, per Cent Positive	Leukocyte Count	Pulse Rate	Blood Pressure		NaCl Test (McClure-Aldrich, Min.)	Reaction to Tuberculin, Mm.		
											Systolic	Diastolic		24 Hours	48 Hours	72 Hours
43.00/57	84	5	41	13	0	+1.7	0	66	9,700	83	121	71	72	6	6.7	3.6
38.00/62	100	5	28	16	0	+0.8	14	43	11,800	77	100	65	70	7.8	9	5
41.00/58.4	94	4.4	38	10.4	0	+9.2	0	38	11,900	86	120	72	75	7.4	4.1	2.4
39.25/60.75	100	4.5	33	13	0	+3.4	0	50	13,008	89	117	73	78	9	4	1.6
40.00/60	90	4.3	44	11.5	6	+7.4	31	44	13,000	89	119	70	85	8	8	5
36.30/63.7	85	4.2	39	10.3	5	+14	22	44	13,300	97	118	70	75	8.4	7	4.5
39.30/60.7	97	2.9	40	11.8	20	+15	40	20	10,500	104	113	75	93	8.6	9	4.8

Persons and of "Normal" Persons on the Basis of the Weight Curves

Pulse Pressure, per Cent	Pulse Pressure × Pulse Rate, per Cent	CO ₂ Combining Power	Reaction to Ice, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg. per 100 Cc.	Leucithin, Mg. per 100 Cc.	Sputum, per Cent Positive	Tuberculosis Fixation, per Cent Positive	Darányi Reaction, per Cent Positive	Endothelial Reaction, per Cent Positive	Leukocyte Count	Increase in Leukocyte Count after Intracutaneous Injection of Aolin, per Cent	Corpuscles/Plasma Ratio	Tuberculin Reaction, Mm.			NaCl Test (McClure-Aldrich), Min.
															24 Hours	48 Hours	72 Hours	
15	21.6	56	14.7	38.3	229	211
21	26	57.1	16.8*	42	221	226
11	23	58.8	21	58.7	215	208
-5	-5	57.5	12	28.6	195	199	16.3	43	60	73	43	10,680	5	38.2/61.6	8	7	4.7	85
-4	0	55.3	12	32.7	197	200	16.7	46	46	60	37	12,900	4	40.8/59.2	8.1	7.1	3.4	77
-5	-5	55.8	10	33.2	180	198.3	15.4	77	61	70	30	11,400	1	40.5/59.5	7	4.8	2	62

In order to investigate further some of the interrelations of the resistance and the chemical status of these persons, we made a study of eighty-three patients of the Municipal Tuberculosis Sanitarium. The patients (all men) in various stages of clinical activity and progression were selected so as to give us a fair cross-section. In table 1 are recorded the serial number of each patient, his age, his clinical status, the x-ray diagnosis and the complications.

ANALYSIS ON THE BASIS OF THE CLINICAL CLASSIFICATION

In table 2, we present summaries of the results of the examinations of the patients with tuberculosis when arranged on the basis of clinical classifications. It is unnecessary to point out that an analysis on such a basis affords little insight into any actual correlation between resistance and the chemical and autonomic status of the patient. A case of far advanced tuberculosis may be one that is chronic, and associated with

TABLE 4.—Results of Examinations of Patients Who Were in Good

Patient	Diagnosis	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds	CO ₂ Combining Power
55	M.A. B.	6.5	82	12.6	12.0	21.5	1.66	40	10.7	100	10	61.2
16	Min. A.	13	69	5.3	26	8.16	60	12	51.4
6	Min. A.	6	56.1	9.3	9.4	14.2	1.5	17	8.77	20	12	56.8
21	Min. A.	7	64.1	9.5	8.8	19.4	2.2	30	6.96	110	16	58.5
80	Min. B.	6.5	64	9.8	9.97	19	1.9	12	7.91	...	12	51.8
79	M.A. A.	9	67.2	7.4	11.5	17.5	1.5	20	8.94	...	18	55.5
39	M.A. B.	10.5	69.4	6.1	9.3	16.3	1.75	26	7.73	175	10	56.9
27	M.A. A.	9	51.9	5.7	13.1	15.2	1.16	22	9.64	140	7	58
43	F.A. B.	6	69.2	11.5	3	6.71	60	5	56.8
46	F.A. B.	6	72.8	12.1	9.9	22.5	2.27	42	9.35	90	12	55
44	F.A. A.	7	80.9	11.5	32	7.41	78	5	48.4
45*	F.A. A.	7	65.1	8.6	11.8	20.6	1.74	40	9.45	100	20	56.9
76	F.A. B.	6.5	70.9	10.9	12.5	19.45	1.55	65	9.87	...	15	60.9
82	F.A. A.	8	61.2	7.6	9.4	17.7	1.87	25	12	...	12	49.4
52	F.A. B.	6	57	9.5	9.6	19.3	2.1	100	11.5	75	2
71	M.A. B.	6	75.9	12.6	12.2	19.1	1.57	38	7.63	...	17	64
16	Averages....	7.5	67.3	9.37	10.7	18.5	1.75	33	8.92	91.6	11.5	56.1

* Died, 1929.

relatively high resistance; a case of minimal manifestation of the disease, one that may go on to death in a relatively short time.

When we examine these averages, we find no consistency. While the permeability of the capillaries of the skin ranges from 63 in the patients with the minimal manifestations to 77 in the patients with the far advanced conditions, the intermediary groups show no progressive relation. In general, calcium increases; but here, too, there is no consistent progression. Potassium diminishes, as do lecithin and the CO₂ combining power, but all the averages are irregular. As is to be expected, the Darányi reaction, the globulins, the complement fixation and the basal metabolic rate increase in fairly consistent fashion.

ANALYSIS ON THE BASIS OF THE WEIGHT CURVE

The analysis based on the weight curve of the patient might offer a better approach and in table 3 we present such a summary. Two patients of the series are not included because of the briefness of the period of observation at the sanitarium. For purposes of comparison, we present first the averages for the truly normal persons, those showing roentgen evidence of "healed" tuberculosis and those showing roentgen evidence of "active" tuberculosis of our series of 100 "normal" men.

Condition When Examined and Who Improved During the Two Years Following

Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
							24 Hours	48 Hours	72 Hours		
Vagotonic	18	14	7	8	1.6	85	17	5	5	—	38.2
Sympatheticotonic	15	2.1	3	0	1.12	90	0	0	0	—	36.3
Vagotonic	15	6.7	10	7.5	1.02	80	8	10	0	—	40.5
Vagotonic	17	8.7	4	0.5	0.94	77	5	4	4	—	42.8
Sympatheticotonic	18.7	7.8	10	2.5	1.32	60	12	12	12	—	34.2
Sympatheticotonic	12.2	6.3	10	2.5	1.77	70	5	4	4	++++	32.4
Vagotonic	13.5	7.6	10	2	1.53	95	20	6	0	A.C. ?	39.4
Vagotonic	15.2	2.8	8	1.5	1.38	77	8	6	0	++	52.05
Vagotonic	14.5	11.7	6	2	1.38	120	12	25	25	+	35.7
Vagotonic	18	12.6	10	0	1.3	60	5	10	14	++	26.8
Vagotonic	16.2	8.7	12	0	1.51	105	8	15	14	++	45
Vagotonic	16.5	9.7	10	10	1.41	62	9	11	13	++++	32.9
Sympatheticotonic	10	11.6	10	0	75	8	8	8	++	35.4
Vagotonic	16	4.7	12	0	1.15	120	8	6	4	+	34.6
Vagotonic	13.7	17	10	10	1.5	115	10	3	3	+++	46.5
Sympatheticotonic	17	3.7	12	0	75	5	5	3	+
11 V., 5 S.	15.4	8.4	9	1.7	1.35	84.7	8.7	8.1	6.8	4 —, 11 +, 1 A.C.	38.7

When we examine the averages for the tuberculous patients, we apparently approach certain correlations of significance. It will be observed that the permeability of the capillaries increases and the blood calcium diminishes (as does the K/Ca ratio). The Kromayer light erythema time, the ice reaction time and the NaCl test (McClure-Aldrich) time are lessened, as we pass from the gaining to the losing groups. In a previously published analysis,² we showed the differences in the curves of the blood pressure following the injection of epinephrine and the change in the leukocyte count following injections of a non-specific milk preparation in these groups of patients. These curves

2. Petersen, W. F., and Levinson, S. A.: *Am. Rev. Tuberc.* **18**:616 and 839, 1928.

TABLE 5.—Results of Examinations of Patients Who Were

Patient	Diagnosis	Weight	Condition at Time of Writing	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent
53	M.A. B.	Stationary	Losing	6	71.5	11.5	12.9	24	1.85	45	8.8
63	F.A. C.	Gaining	Losing	7	82	11.7	10.2	17.2	1.68	38	9.9
60	F.A. B.	Gaining	Dead	6	67	11.1	10	13.9	1.39	60	9.35
49	M.A. B.	Gaining	Dead	7.5	44	5.8	8.6	22.4	2.6	40	9.9
83	F.A. B.	Gaining	Dead	6	74.7	12.4	13.1	21.6	1.65	23	8.67
67	F.A. B.	Gaining	Losing	6	58	9.6	11.6	19.2	1.66	60	10.7
64	F.A. B.	Gaining	Dead	6	56.4	9.4	12	19	1.59	30	10.0
68	M.A. A.	Gaining	Dead	9	32	3.5	10.6	14.3	1.35	20	8.06
34	F.A. B.	Stationary	Dead	7	42	6.1	9	19.1	2.13	28	8.6
58	F.A. B.	Gaining	Stationary	7	45	6.4	11	17.4	1.57	17	11
56	M.A. A.	Gaining	Stationary	8	67	8.3	8.6	18.1	2.1	15	7.70
Averages.....				6.8	58.1	8.7	10.6	18.7	1.77	34.2	9.30

TABLE 6.—Results of Examinations of Tuberculous Patients

Patient	Diagnosis	Condition at Time of Examination	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.
37	M.A. A.	Arrested	9	60.7	6.7	11.4	23.7	2.08	10	8.7	33
41	F.A. B.	Improved	7.5	78	10.4	34	7.85	147
75	F.A. A.	Improved	6	62.3	10.3	10.3	17.6	1.71	100	9.33	...
77*	F.A. B.	6	43	7.1	10.8	21.6	1.98	5	12.9	...
73	M.A. B.	Improved	6	63.1	10.5	11.6	17.6	1.53	35	9.35	...
65	M.A. A.	Quiescent	12.2	23.8	1.96	23	9.56	110
42	F.A. B.	6	65	10.9	9.5	16.6	1.75	50	10.4	60
62	F.A. A.	Well	6	69	11.5	8.2	14.4	1.75	7	7.73	85
70	F.A. B.	Stationary	6	37.7	6.2	13.4	23.9	1.79	45	11.27	...
59	F.A. B.	6	68.4	11.4	15	9.35	190
19	F.A. A.	Wassermann ++	8	56	8.3	8.8	18.9	2.15	22	7.98	50
30	M.A. A.	Quiescent	6	88	14.6	10.8	17	1.57	40	7.91	170
23	F.A. A.	8	76	9.5	9.5	23.1	2.43	30	8.56	140
24	M.A. B.	Quiescent	8.5	72	8.4	8.4	24.5	2.92	10	7.85	80
32	F.A. A.	Arrested	7	72.1	10.3	9.5	15.6	1.64	25	8.28	142
40	F.A. B.	Quiescent	7.5	69.3	9.2	8.8	22.4	2.55	45	6.43	70
38	F.A. B.	Arrested	7	65.6	9.3	9.3	26.8	2.89	10	8.09	130
29	Min. A.	Arrested	9	60.7	6.7	11	18.9	1.69	25	8.7	237
1	M.A. A.	Improved	8	74	9.3	10.2	15.2	1.51	5	7.65	45
5	M.A. B.	Stationary	8.5	75	8.3	9.1	15.4	1.69	32	8.5	90
Averages.....			7.1	66.4	9.44	10.1	19.8	1.97	28.4	8.517	111

* Died, 1929.

Doing Well When Examined but Who Subsequently Grew Worse

Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds	CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheel, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheel, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Mm.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
										24 Hours	48 Hours	72 Hours		
120	15	51.9	Vagotonic	15.7	7	12	0	1.30	90	7	8	4	+++	38.4
85	12	53.5	Vagotonic	14.2	6.7	12	0	1.21	130	10	10	0	—	44.3
25	10	59.8	Sympatheticotonic	13	4.2	9	3.5	1.16	35	6	5	4	+++	37.1
78	19	57.3	Vagotonic	7.2	8	10	2.5	1.04	85	10	9	0	+++	35.5
40	8	56.3	Vagotonic	20.7	6.5	10	4	45	21	12	8	—	32.1
40	23	58.9	Sympatheticotonic	16.5	10.1	12	1	1.05	30	4	4	6	++++	34.6
65	15	56.3	Sympatheticotonic	17.7	8.1	10	5	1.23	90	11	3	2	++++	38.2
110	15	55.4	Sympatheticotonic	8	4.7	14	0	1.22	110	8	8	6	—	38.1
71	1	62.7	Sympatheticotonic	13.7	6.6	10	9	1.62	85	8	0	0	+++	42.9
65	6	65	Vagotonic	16	4.5	12	0	1.4	159	7	15	8	—	19
85	10	59.4	Vagotonic	10.7	8.2	12	0	1.32	120	10	6	6	++++	48.8
74.4	12.1	57.8	6 V., 5 S.	13.9	6.7	11.1	2.27	1.25	89	9.2	6.8	4	7 +, 4 —	37

in Whom Disease Was Stationary and Remained So

Reaction to Ice, Seconds	CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheel, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheel, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Mm.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
									24 Hours	48 Hours	72 Hours		
7	58.7	Vagotonic	16.7	9.5	7	1.5	1.25	85	2	5	8	—	43.2
12	49.8	Vagotonic	15.5	6.6	6	5	1.53	85	10	25	8	—	37.5
18	53.5	Sympatheticotonic	10.75	7.25	6	0	1.30	145	28	12	6	++++	34.3
25	55.4	Vagotonic	11.5	5	14	0	1.35	83	11	8	6	++++	31.1
15	59.3	Vagotonic	18.25	5.75	13	1.5	1.15	60	6	8	4	+++	36.05
12	...	Vagotonic	11.7	5.7	7	0	1.38	85	8	5	3	+	45.1
20	63.8	Vagotonic	17.5	11.8	7	14	1.73	75	12	10	3	—	46.7
30	47.9	Vagotonic	17.5	4.75	15	0	1.07	85	12	22	0	+++	54.2
3	52.9	Vagotonic	5.2	3.1	6	0	1.03	68	6	7	8	++	40.1
10	53.7	Sympatheticotonic	7.5	3.1	11	2	1.3	80	5	10	0	—	29
12	54.4	Vagotonic	19.2	6.6	5	10	0.92	92	7	7	0	+	44.5
15	51.4	Sympatheticotonic	25.5	10.2	10	0	1.05	..	14	3	0	—	36.4
8	68	Sympatheticotonic	12.5	6.3	5	1.5	1	40	3	3	0	++++	41.3
5	66	Sympatheticotonic	15.5	6.6	9	3	1.09	190	5	0	0	—	41.1
12	43.9	Vagotonic	18.5	8	20	5	0.98	..	3	0	0	—	47.1
8	56.9	Vagotonic	17	5.8	10	5	1.84	35	0	0	0	++	43.1
5	57.2	Vagotonic	23.7	9.5	10	12.5	1.43	80	0	0	0	+	35.1
8	40.1	Vagotonic	14	6.75	4	3	0.95	65	10	6	7	—	51.1
15	58.6	Vagotonic	17.5	6.5	9	0	1.06	..	0	0	0	—	42
15	57.2	Vagotonic	7.7	3	6	0	1.05	70	20	0	..	—	45.2
12.7	55.1	15 V., 5 S.	15.16	6.59	9	3.2	1.233	83.7	8.8	6.5	2.6	10 +, 9 —	41.2

showed a consistent increase in the vagotonic effect in the losing groups. The mathematical calculation of the pulse pressure following the injection of epinephrine shown in table 3 merely indicates the decided difference existing between the actively tuberculous groups and the

TABLE 7.—Results of Examinations of Tuberculous Patients Who

Patient	Diagnosis	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds	CO ₂ Combining Power
22	M.A. A.	7.5	51.7	10.8	9.5	22.1	2.33	29	7.1	18	2	74
33	M.A. B.	8	62	7.7	10	16.3	1.63	25	7.8	75	15	53.7
36*	F.A. A.	6	76	12.6	9.9	26.2	2.67	43	8.9	111	12	55.3
51	M.A. B.	5.1	68.5	9.7	9.9	20.3	2.05	80	10.5	90	8	66.8
Averages.....		6.6	72	10.4	9.8	21.2	2.17	44.2	8.5	73.5	9.2	62.4

* Died, November, 1928.

TABLE 8.—Results of Examinations of Tuberculous Patients

Patient	Diagnosis	Condition at Time of Writing	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds
9	M.A. A.	Dead	8	72.4	8.04	10.2	19.1	1.87	9	8.28	15	12
18	F.A. A.	Dead	8	75	9.4	8.4	21.7	2.58	75	8.8	10	3
61	F.A. C.	Dead	6	69	11.5	10.5	18.8	1.79	43	10.2	30	10
47	F.A. A.	Dead	6.4	73	11.2	10.9	20.3	1.85	28	9.45	105	12
66	F.A. C.	Dead	8	82	11.5	10.2	19.6	1.92	80	9.66	95	16
60	F.A. C.	Dead	7.5	79	10.5	11.1	19.2	1.73	48	8.70	90	20
78	M.A. B.	Dead	7	73	10.7	10.4	19.2	1.84	15	9.87	...	13
48	M.A. B.	Dead	7.5	62.5	8.2	8.5	16.2	1.91	40	9.92	115	8
74	F.A. B.	Dead	6	58	9.6	10.1	17.9	1.72	46	8.06	...	5
28	F.A. A.	Dead	7	75	10.7	50	8.92	163	9
25	F.A. A.	Dead	8	74	9.3	9.9	15.4	1.56	67	7.73	98	12
7	M.A. B.	Dead	8.5	71	8.3	9	14.3	1.59	31	7.36	8	5
15	F.A. A.	Stationary	8	75	9.3	9.7	19.4	2	32	8.36	40	4
26	M.A. B.	Dead	4.5	70	15.4	11.4	17.3	1.52	35	8.28	193	20
31	Min. B.	Stationary	7	74.2	10.6	12.8	15.7	1.23	42	9.02	156	8
Averages			7.1	72.2	10.2	10.2	18.1	1.70	42.7	8.84	85.6	9.8

group of "normal" persons, the group of persons with "healed" lesions and the group with roentgen evidence of "active" tuberculosis.

On the other hand, the values for globulin follow more consistently the clinical classification, as do those for the Darányi reaction, the complement fixation, the basal metabolic rate, etc.

While the analysis based on the weight curve enables us to reach certain definite conclusions, the weight curve alone is by no means a

criterion of resistance. Apart from the fact that periodic fluctuations may depend solely on fluctuation of the water balance, patients may be gaining at the time of the examination and shortly afterward present a reversal.

Were Losing Weight and Who Subsequently Showed Improvement

Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
							24 Hours	48 Hours	72 Hours		
Vagotonic	15	8.8	6	2.5	1.00	45	8	12	0	++	32.6
Sympatheticotonic	11.5	6.75	8	2	1.6	98	11	0	0	—	39.1
Sympatheticotonic	16.2	6	10	5	...	95	2	0	0	+++++	46.5
Sympatheticotonic	11.5	6.1	10	11.5	1.04	95	12	4	0	+++++	40.7
3 S., 1 V.	13.5	6.8	8.5	5.25	1.43	82	8.2	5	0	3 +, 1 —	30.7

Who Were in Poor Condition and Who Grew Worse

CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
								24 Hours	48 Hours	72 Hours		
62.1	Vagotonic	18	5	6	4.5	1.18	75	0	0	0	—	46
55.1	Sympatheticotonic	17	6.8	5	4	1.06	45	6	7	10	+	34.5
42.5	Sympatheticotonic	15.7	4.7	7	0	1.31	75	5	6	8	+++	45.5
55.2	Vagotonic	10.5	6.3	8	18.5	1.2	105	7	7	7	+	40.7
53.5	Vagotonic	12	8.7	12	0	0.94	75	9	9	7	++	34.3
38.8	Vagotonic	15.2	5.5	10	0	1.18	65	7	5	3	—	51.1
57.5	Sympatheticotonic	12.5	6	10	1	1.33	18	8	0	3	—	37.1
57.2	Vagotonic	15.2	13	9	11	1.05	90	8	4	3	++++	44.1
60.3	Vagotonic	15	5.7	14	0	1.24	48	9	3	0	+	34.8
59.2	Vagotonic	23.5	5.3	8	0	1.1	80	7	3	0	+++	36
51.8	Vagotonic	12.7	5.6	10	5.5	1	87	7	0	0	+++	30.9
57.2	Vagotonic	17	5.7	4	5.5	1.13	40	5	0	0	—	37.3
62.5	Vagotonic	20.5	6	9	2.5	1.12	50	0	0	0	—	37.7
57.2	Vagotonic	11.25	5.7	5	7.5	1.17	52	4	0	0	+++	38
57.2	Vagotonic	14.5	5.37	10	5	1.05	15	5	0	0	—	46.1
55.1	12 V., 3 S.	15.37	6.35	8.4	4.3	1.17	61.3	5.8	3.3	2.7	9 +, 6 —	39.6

SUMMARY BASED ON PROGNOSIS

The patients of the series studied were examined during the summer of 1927. As all were sanitarium patients, it was possible to follow the clinical course of the disease in each and to analyze the results of the examinations on the basis of the condition in 1929. In tables 4 to 8, we present the results of the more important examinations of these patients when so classified.

When we examine the summaries in table 9 certain deductions appear warranted.

Lower Capillary Permeability in Patients with Good Prognosis.

—While occasionally increased permeability is found in persons of this type (no. 44 and 55 in the group who were gaining—both, however, with pleuritic effusion), generally, as we showed previously, it goes hand in hand with progression of the disease, while persons with silent lesions (the ones with roentgen evidence of active tuberculosis in the series of 100 "normal" men) have low permeability.

TABLE 9.—*A Summary of the Results of Examinations*

Table	Number in Group	Condition at Time of Examination	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent
4	16	Good; continued improvement....	7.5	67.3	9.3	10.7	18.5	1.75	33
5	11	Good; later poor.....	6.8	58.1	8.7	10.6	18.7	1.77	34
6	20	Stationary.....	7.1	66	9.4	9.1	19.8	1.97	38
7	4	Poor; later improved.....	6.6	72	10.4	9.8	21	2.17	44
8	15	Poor; continued extension.....	7.1	72	10.2	10.2	18.1	1.79	42.7

For many reasons, a question of utmost importance immediately comes up. Is the increased capillary permeability that is associated with poor prognosis and progression of the disease due to the clinical condition or does the increased permeability bring about the progression? If the former, we deal merely with an incident of clinical observation; if the latter, we have at our command an approach to one of the factors in therapeutic control. This is discussed in part VIIC. The clinical association is obviously close. In the group who were doing well when first examined and who later showed decline (table 5), the capillary permeability was low. In the group who were doing poorly when first examined and who showed subsequent improvement (table 7) capillary permeability was high.

The status of the capillary wall—the functional capacity—is obviously a most labile affair, depending not only on the activity of the

local tissue, but on endocrine (probably thyroid-suprarenal-pituitary) and chemical equilibria, as well as on autonomic disturbances. With so many variable factors, one cannot assume any dogmatic position. Certainly, acute intoxications increase the capillary permeability.³ Presumably, tuberculin may diminish as well as increase it.⁴ Progression of the disease might logically be expected to increase permeability. On the other hand, there is evidence to support the view that the status of the capillary may be the predetermining factor on which either fixation or dissemination depends. We have mentioned the relation to

of Tuberculous Patients (Tables 4 to 8)

Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma	
							24 Hours	48 Hours	72 Hours			
11 Vagotonic												
5 Sympatheticonic	= 30%	15.4	8.4	9	2.6	1.35	84.7	8.7	8.1	6.8	70	38.7
6 Vagotonic												
5 Sympatheticonic	= 45%	13.7	6.7	6.7	2.2	1.25	80	9.2	6.8	4	63	37
15 Vagotonic												
5 Sympatheticonic	= 23%	15.1	6.6	9	3.2	1.22	83.7	8.6	6.5	2.6	52	41.2
1 Vagotonic												
3 Sympatheticonic	= 70%	13.5	6.8	8.5	3.2	1.43	82	8.2	5	0	75	30.7
12 Vagotonic												
3 Sympatheticonic	= 20%	15.3	6.3	8.4	4.3	1.17	61.3	5.8	3.3	2.7	60	30.6

season. A similar case may be made out for the menstrual cycle, for remote trauma and for inanition. But, again, we must not forget that in thyroid disease, with its accompaniment of greatly increased permeability, no direct relation to activation of tuberculosis exists.

Lowered Inflammatory Index in Cases with a Favorable Prognosis.—While the differences are not great, the grouping shows conclusively that the inflammatory response of the skin in patients doing well is seemingly diminished. In the introductory paragraphs, we presented our reasons for believing that such a lowering of the inflammatory response may be of benefit to the patient in protecting him from too

3. Petersen, W. F.: Permeability of Skin Capillaries in Various Clinical Conditions, *Arch. Int. Med.* **39**:19 (Jan.) 1927.

4. Petersen, W. F., and Levinson, S. A.: *Am. Rev. Tuberc.* **8**:122, 1923; *J. Immunol.* **8**:387, 1924.

great an absorption of toxic material. Many coordinated problems enter into consideration, because certain types of tuberculous lesions may be observed in which inflammatory response may be most useful (skin, etc.). Generally speaking, the clinician has tried to build up a resistance to inflammatory response, either by immunizing his patient until the reaction of the skin has diminished in intensity or by using non-specific methods to bring about the same result. The therapeutic goal in common practice is distinctly inhibitory, even when brought about by the methods which may transiently accelerate the inflammatory response.

High Blood Calcium Level in Cases with Good Prognosis.—The explanation of the calcium values is, we believe, relatively simple. The cases with good prognosis have a high level; with progression this declines. In cases that have a poor prognosis, calcium is evidently swept into the serum from the tissues and raises the level in the serum. We have already seen that there is no relation of the calcium level to the clinical status when the results of the examinations of the patients are arranged on the basis of the classification made by the National Tuberculosis Association. When the results are arranged on the basis of the weight curve, the patients who are gaining show a higher calcium level. There appears to be no necessary relation to the K/Ca ratio.

High Serum Globulin in Cases with Poor Prognosis.—As an index of activity, the increase in globulin—and with it a coincident increase in the degree of positiveness in such a reaction as the Darányi reaction—is, as might be expected, clearcut. The concentration of serum protein, is, on the other hand, not particularly characteristic.

Apparently Sympatheticotonic Reactions to Epinephrine.—In a previous study of the curves of the reactions of these patients to epinephrine, we called attention to the fact that when the results are grouped on the basis of the weight curve, the patients who are gaining are shown to have a less marked vagotonic reaction than those have who are losing. In the tables here presented, we have merely indicated the general character of the curves by designating those as sympatheticotonic in which a primary increase in the systolic blood pressure can be ascertained in the first fifteen minutes after a subcutaneous injection of epinephrine hydrochloride.

In our series of 100 "normal" men, approximately 40 per cent give a distinctly sympatheticotonic reaction.⁵ In the tuberculous group, 32 per cent were so classified. But when we estimate effects on the basis of the actual increase in pulse pressure, the 100 "normal" men show an

5. Petersen, W. F., and Levinson, S. A.: Am. Rev. Tuberc., to be published.

6. Petersen, W. F.; Levinson, S. A., and Arquín, S.: Relation of Reaction to Epinephrine to Potassium Calcium Ratio and Other Ratios, Arch. Int. Med. 42: 256 (Aug.) 1928.

average increase of approximately 14 per cent during the hour after the injection, while the tuberculous persons show an actual loss of 5 per cent.

In general, it appears that there are more sympathetotonic reactions among the patients with favorable prognoses. We desire, however, that this conclusion be regarded with reservation. The reactions to epinephrine by no means conform to the fixed or rigid outlines formerly accepted. When one examines the individual curves, one is rather struck by the irregularity in the tuberculous person as compared with the "normal" person. We believe that this is an expression of the general autonomic instability. In the series of four patients who were losing and who later improved (table 7) there is an observation that may be of some significance. Of the four, three had a distinctly sympathetotonic reaction. Whether this presaged the later favorable development we do not know.

The Bearing of the Intracutaneous Reactions.—Of the intracutaneous reactions, only the flare due to the injection of thyroxin seems to be of interest. The persons with favorable prognoses appear to be less reactive. This may be in line with the general diminution of the inflammatory reaction; it may be related to the same phenomena that underlie the delay in their reaction to ice and the lessened permeability of their capillaries (see table 1 part I).

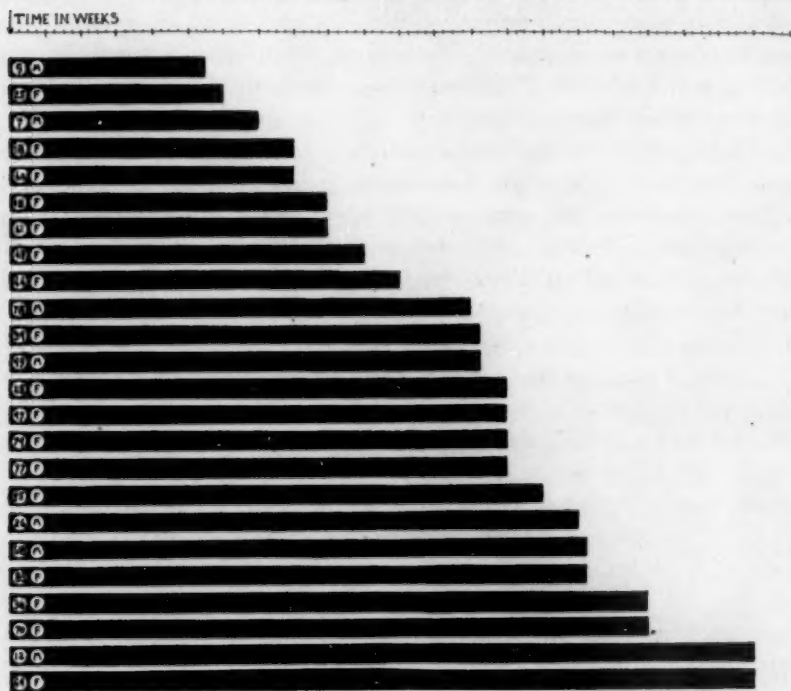
Larger Value for the Cholesterol/Lecithin Ratio in Persons with Favorable Prognoses.—A distinct correlation exists between the clinical condition and the cholesterol/lecithin ratio, an exception being found only in the group shown in table 7. Here a high value of the ratio existed with a declining weight curve at the time of examination. Just as with the reaction to epinephrine the possibility exists that this reaction is of some prognostic significance. The assumption that the outcome of the reaction to epinephrine may depend on the cholesterol/lecithin ratio is unfounded. Our sympathetotonic patients show both high and low values for this ratio.

Shortening of the McClure-Aldrich Sodium Chloride Disappearance Time in the Cases with "Poor" Prognosis.—This is apparent in the tables in which the results are arranged in accordance with the weight curve, as well as in the final arrangement on the basis of prognosis. On the other hand, the fallacy inherent when only the N. T. A. clinical classifications are used becomes apparent when we study table 1. Here the far advanced "C" cases (five in number) have an average disappearance time of 93 minutes, i.e., longer than that of any of the other groups. However, the three members of this group who died had a 75 minute disappearance time, while the two still living had a prolonged time of 130 and 110 minutes, respectively. The average, of course, gives an entirely wrong impression. It would appear that the reaction might serve a useful purpose in the prognosis.

Cases with Favorable Prognosis Characterized by a More Marked Reaction to Tuberculin.—Both in the size of the wheal and in the persistence of the infiltration, the patients with the favorable prognoses reveal a considerable accentuation. On the other hand, there is no characteristic difference in the circulating antibodies (complement fixation) nor any striking difference in the corpuscle/plasma ratio.

ANALYSIS OF RESULTS IN FATAL CASES

Finally, we present an analysis of the results of the examinations in cases that have terminated fatally. During the twenty months that elapsed between the time of the examination and the time of this analysis,



to be contrasted with that for the group of twelve who died later. The total period of clinical activity until the time of death averaged 45 months for the former group and 65 months for the second group.

An examination of the table indicates the following: The first group, the short lived ones, had the more permeable capillaries (67 as compared

TABLE 10.—*Results of Examinations of Patients with Fatal Tuberculosis, One Group Short Lived and the Second Group Longer Lived*

Patient	Total Time of Activity Until Death, Mo.	Capillary Permeability	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Cholesterol, Mg. per 100 Cc.	Lecithin, Mg. per 100 Cc.	Reaction to Tuberculin			NaCl Test (McClure-Aldrich), Min.	Reaction to Ice, Seconds	Reaction to Epinephrine
									24 Hours	48 Hours	72 Hours			
9	29	72	10.2	19.1	1.87	9	208	17.5	0	0	0	75	2	Vagotonic
25	35	74	9.9	15.4	1.56	67	171	17.1	7	87	12	Vagotonic
7	14	71	9	14.3	1.59	31	190	16.7	5	40	5	Vagotonic
18	13	75	8.4	21.7	2.58	75	167	15.8	6	7	10	45	3	Sympatheticotonic
60	35	79	11.1	19.2	1.73	48	196	16.6	7	5	3	65	20	Vagotonic
48	75	62.7	8.5	16.2	1.91	49	222	13.4	8	4	3	90	8	Vagotonic
61	75	69	10.5	18.8	1.79	43	230	17.8	5	6	8	75	10	Vagotonic
69	65	67	10	13.9	1.39	60	171	14.7	6	5	4	35	10	Vagotonic
60	50	82	10.2	19.6	1.92	80	163	17.2	9	9	7	75	10	Vagotonic
78	25	73	10.43	19.2	1.84	15	208	13.3	8	6	3	18	13	Sympatheticotonic
34	40	42	9	19.1	2.13	28	167	10.7	8	0	0	85	1	Sympatheticotonic
49	31	44	8.6	22.4	2.60	40	155	14.9	10	9	0	85	19	Vagotonic
Av.	45	67	9.0	18.2	1.9	45	188	15.4	6.0	4.2	3	64	12	9 V./3 S.
28	90	75	50	167	15.1	7	3	0	80	9	Vagotonic
47	50	73	11.2	20.3	1.85	28	167	13.9	7	7	7	106	12	Vagotonic
74	50	58	10.1	17.9	1.72	46	196	15.7	9	3	0	48	5	Vagotonic
77	62	43	10.8	21.6	1.98	5	278	20.6	11	8	6	83	25	Vagotonic
45	41	66	11.8	20.6	1.74	40	206	14.7	9	11	13	62	20	Vagotonic
26	55	70	11.4	17.3	1.52	35	185	15.8	4	0	0	52	20	Vagotonic
68	31	32	10.6	14.3	1.35	20	238	19.5	8	8	6	110	15	Sympatheticotonic
83	47	74	13	21.6	1.65	26	167	21	12	8	45	8	Sympatheticotonic
36	92	76	9.9	26.2	2.67	43	2	4	0	95	12	Sympatheticotonic
70	130	37.7	13.4	23.9	1.79	45	167	16.1	6	7	8	68	3	Vagotonic
12	80	72	10.7	19.2	1.79	32	208	20.8	6	0	0	55	4	Sympatheticotonic
64	45	56	12	19.1	1.59	30	208	16.8	11	3	2	90	15	Sympatheticotonic
Av.	65	61	11.4	20	1.8	34	199	16.9	8.5	5.5	4.1	74	15	7 V./5 S.

with 61). They have a lower level of blood calcium (9.9 as compared with 11.3) and less potassium (18.2 as compared with 20), but a slightly higher value for the K/Ca ratio. The serum globulins are increased 45 per cent as compared with 34 per cent, while both the cholesterol and the lecithin levels are lower. The reaction to tuberculin is less marked (6.6, 4.2 and 3 mm. for twenty-four, thirty-six and seventy-two hour readings, as compared with 8.4, 5.5 and 4.1 mm.). The McClure-Aldrich sodium chloride disappearance time is shorter, as is also the time of the reaction to ice.

When we turn to the reaction to the subcutaneous injection of epinephrine hydrochloride, the results in the cases of rapidly fatal disease are of considerable interest. The results are preponderatingly vagotonic, while those in the cases in which the patients lived longest were generally sympathetictonic.

B. DETAILED STUDY OF THE REACTIONS OF PERSONS WITH TUBERCULOSIS

CONTENTS

Blister Time
Permeability of the Capillaries
Inflammatory Index
Calcium, Potassium and the K/Ca Ratio
Protein
Globulin
Basal Metabolic Rate
Vascular Reactions to Epinephrine
CO ₂ Combining Power
Cholesterol
Lecithin
Cholesterol/Lecithin Ratio
Corpuscles/Plasma Ratio
Ice Reaction Time
Kromayer Light Reaction Time
McClure-Aldrich Salt Solution Test
Rumpel-Leede Endothelial Reaction
Intracutaneous Reactions to
Epinephrine
Thyroxin
Reaction to Tuberculin, at Twenty-Four, Forty-Eight and Seventy-Two Hours
Tuberculosis Complement Fixation

BLISTER TIME

In a study of the blister time of tuberculous persons in relation to our group of 100 "normal" men, we pointed out that the persons with roentgen evidence of active tuberculosis (chronic) have, in general, a longer blister time; and in a previous study,¹ we demonstrated that the blister time of those with moderately advanced tuberculosis was prolonged over that of the 100 "normal" men, but that, with advance of the disease, the blister time shortened progressively. The average blister time of our group of 100 "normal" men was 7.5 hours; for the twenty truly normal persons in this group, it was 6.8 hours. For those with roentgen evidence of active tuberculosis, it was 8.4 hours, and for the group of eighty-three tuberculous patients it was 7.4 hours.

To obtain a survey of the relation of the blister time of the tuberculous patients to the clinical status and to the status in the other tests,

1. Levinson, S. A., and Petersen, W. F.: *Am. Rev. Tuberc.* **15**:681, 1927.

we have prepared chart 1, as well as a table of averages for the results of the examinations of the twenty persons with the shortest, and the twenty with the longest blister time.

Explanation of Charts.—As chart 1 is typical for the other charts of this series, we shall explain it in some detail:

The original blister time curve for the clinical material used in the study reported in part III has been retained. It begins with an individual blister time of 3.5 hours and ends with a group blister time of 15 hours. The diamond indicates the range of the blister time of the truly normal persons, extending from a "low" of 6 to a "high" of 9 hours. In addition, symbols at the bottom designate the position on

TABLE 1.—Comparison of the Groups with the Short, the Medium and the Long Time for the Appearance of the Cantharides Blister, with Regard to Clinical Status

Clinical Classification of Patients	Short Blister Time (20 Patients)	Medium Blister Time (37 Patients)	Long Blister Time (20 Patients)
As to Type of Tuberculosis			
Minimal.....	10%	10%	25%
Moderately advanced.....	25%	27%	45%
Far advanced.....	65%	57%	20%
	100%	100%	100%
As to Prognosis			
Good.....	25%	27%	50%
Fair.....	40%	35%	20%
Poor.....	35%	38%	30%
	100%	100%	100%
As to Weight Curve			
Gaining.....	45%	55%	45%
Stationary.....	45%	40%	30%
Losing.....	10%	19%	25%
	100%	100%	100%

this original curve of the truly normal persons and these showing healed and those giving roentgenologic evidence of active tuberculosis.

On this original curve, we have superimposed the curve of the determinations made on the eighty-three tuberculous patients, and have recorded their individual numbers on the curve. Adjacent symbols indicate (X) the death of the patient² or (#) that there was pleural effusion.

In the horizontal columns at the top of the curve, we have indicated the clinical status of the patient. For instance, the first patient represented on the curve (no. 26) is recorded as having had a moderately advanced tuberculosis with a poor general prognosis, and as being stationary in weight when examined.

When we examine the curve, we find that the range of the blister time is from 4.5 to 14 hours, that patients with pleural effusion appear

2. Patients 26, 70, 64, 36 and 12 died after the charts were in the hands of the printer. The symbols for these have therefore not been recorded.

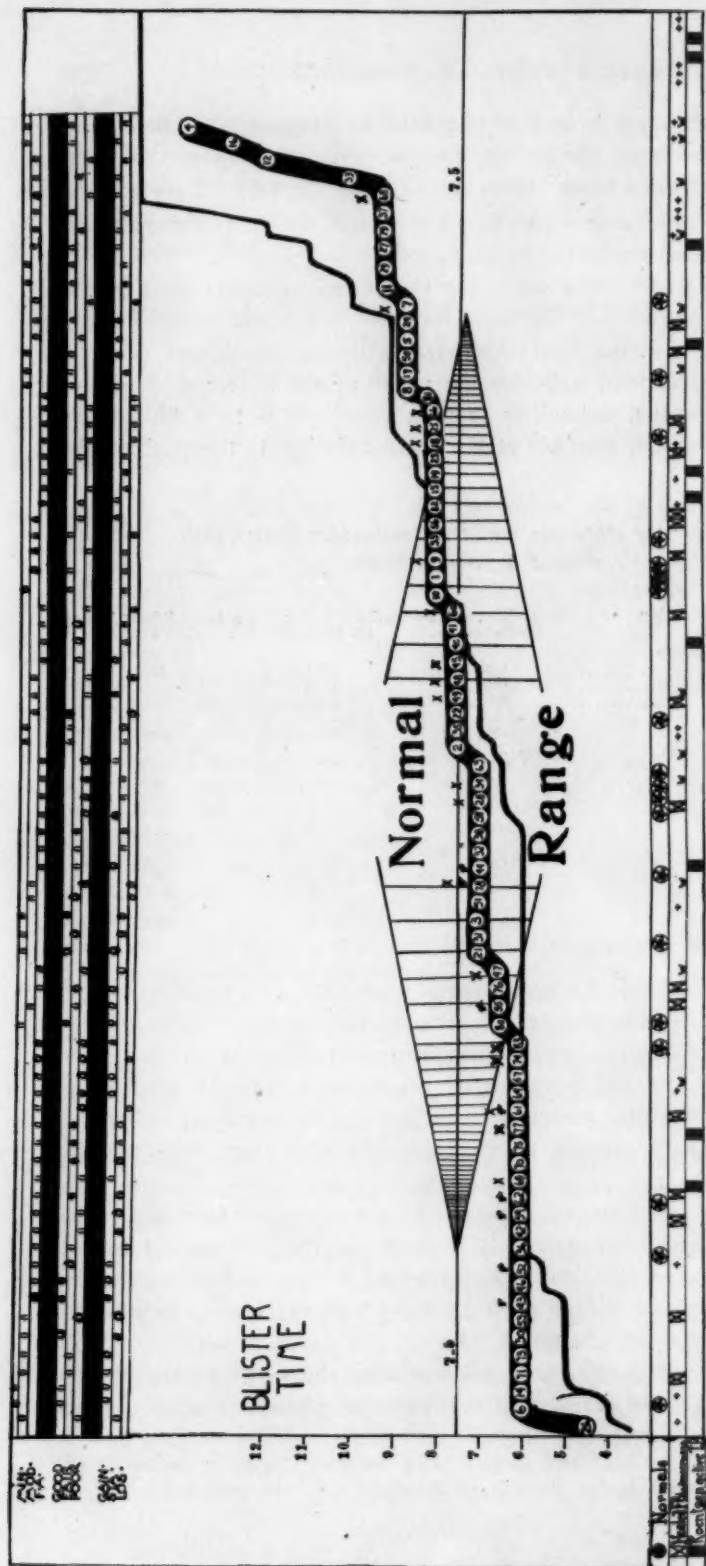


Chart 1.—The blister time curve in patients with tuberculosis. The curve has been superimposed on the original blister time curve for the miscellaneous clinical groups of part III. The original curve begins with a blister time of 3.5 hours, shown by one person, and ends with a blister time of 15 hours, which was shown by a group. The diamond indicates the range of the blister time in the truly normal persons (from 6 to 9 hours). The symbols at the bottom designate the positions on the original curve of the truly normal persons, the persons showing healed tuberculous lesions and those giving roentgen evidence of active tuberculosis.

The individual numbers of the eighty-three patients with tuberculosis are recorded on this curve, the adjacent symbols indicating (X) a patient who died, and (#) one that showed pleural effusion. In the horizontal columns at the top, the clinical status of each patient is indicated. All succeeding charts in this part of the paper are constructed similarly.

at the lower end of the curve and that those who died are apparently uniformly scattered.

In analyzing the results of the examination under consideration in relation to the clinical conditions, we have arbitrarily selected twenty at each end of the curve and have compared them with the middle group. This analysis gives the results shown in table 1. It is evident that the

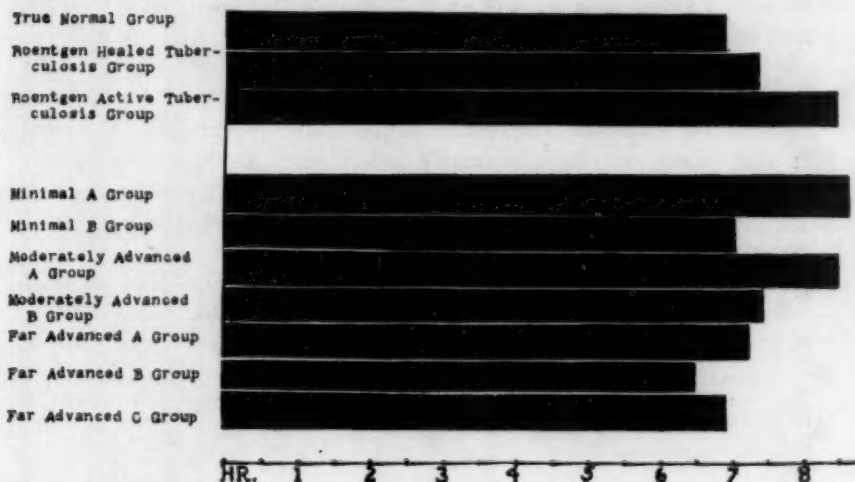


Chart 2.—The blister time curve in the 100 "normal" men of part I.

TABLE 2.—Comparison of the Averages for the Results of the Examinations of the Groups with the Shortest and the Longest Blister Times

Blister Time, Hours	Globulin (per Cent of Total Protein)	Protein, Mg. per 100 Cc.	Ice Reaction, Seconds	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Tuberculin at 24 Hours, Mm.	Deaths
5.92	38.66	9.32	13.9	7.22	9.55	9.4	7
9.3	31.4	8.5	10.8	5.91	7.8	7.5	6

group with the short blister time includes more persons with far advanced tuberculosis, and the group with the prolonged blister time more patients with a good prognosis. In the latter group, the percentage of those losing weight is somewhat greater.

The averages for the more significant reactions of the twenty patients with the shortest blister time are compared with those of the twenty with the longest blister time in table 2.

When we compare the different groups of the 100 "normal" men, as well as the tuberculous groups in relation to blister time, we obtain a picture (chart 2) similar to that which we previously described; i.e., the group with healed tuberculous lesions and the group with roentgenologic evidence of active tuberculosis (the latter chronic and silent) have a longer blister time than have the normal persons. Among the persons with active tuberculosis, those with the minimal and moderate manifestations have a longer time than those in whom the disease is far advanced, whose blister time progressively shortens.

PERMEABILITY OF THE CAPILLARIES

When we examine the permeability curve (chart 3), we note that the cases of the "normal" group that gave roentgenologic evidence of active tuberculosis (lowest horizontal line) are represented in the low range of the curve. On the other hand, those in the series of

TABLE 3.—*Comparison of the Groups with the Low, the Medium and the High Permeability of the Capillaries, with Regard to Clinical Status*

Clinical Classification of Patients	Low Permeability (20 Patients)	Medium Permeability (37 Patients)	High Permeability (20 Patients)
As to Type of Tuberculosis			
Minimal.....	30%	16%	20%
Moderately advanced.....	20%	43%	25%
Far advanced.....	50%	41%	55%
	100%	100%	100%
As to Prognosis			
Good.....	45%	27%	30%
Fair.....	30%	37%	40%
Poor.....	25%	36%	30%
	100%	100%	100%
As to Weight Curve			
Gaining.....	40%	40%	40%
Stationary.....	37%	40%	35%
Losing.....	23%	20%	25%
	100%	100%	100%

eighty-three tuberculous patients, who died, appear in equal numbers at both ends of the curve. However, the duration of clinical activity, as brought out in table 10 of part VII A, is markedly different.

The patients with pleural exudate are, with one exception (no. 52), found toward the upper end of the curve. The association of exudative reactions and increased permeability seems evident.

In examining for the relation between the clinical status and the permeability of the capillaries, percentages were determined as recorded in table 3. No striking differences are revealed in this classification; the group with less permeable capillaries has the largest percentage with good prognosis, but no significant relation of permeability to gain or loss in weight is shown.

Table 4 brings together the averages for the more significant reactions of the twenty persons with low and the twenty with high permeability.

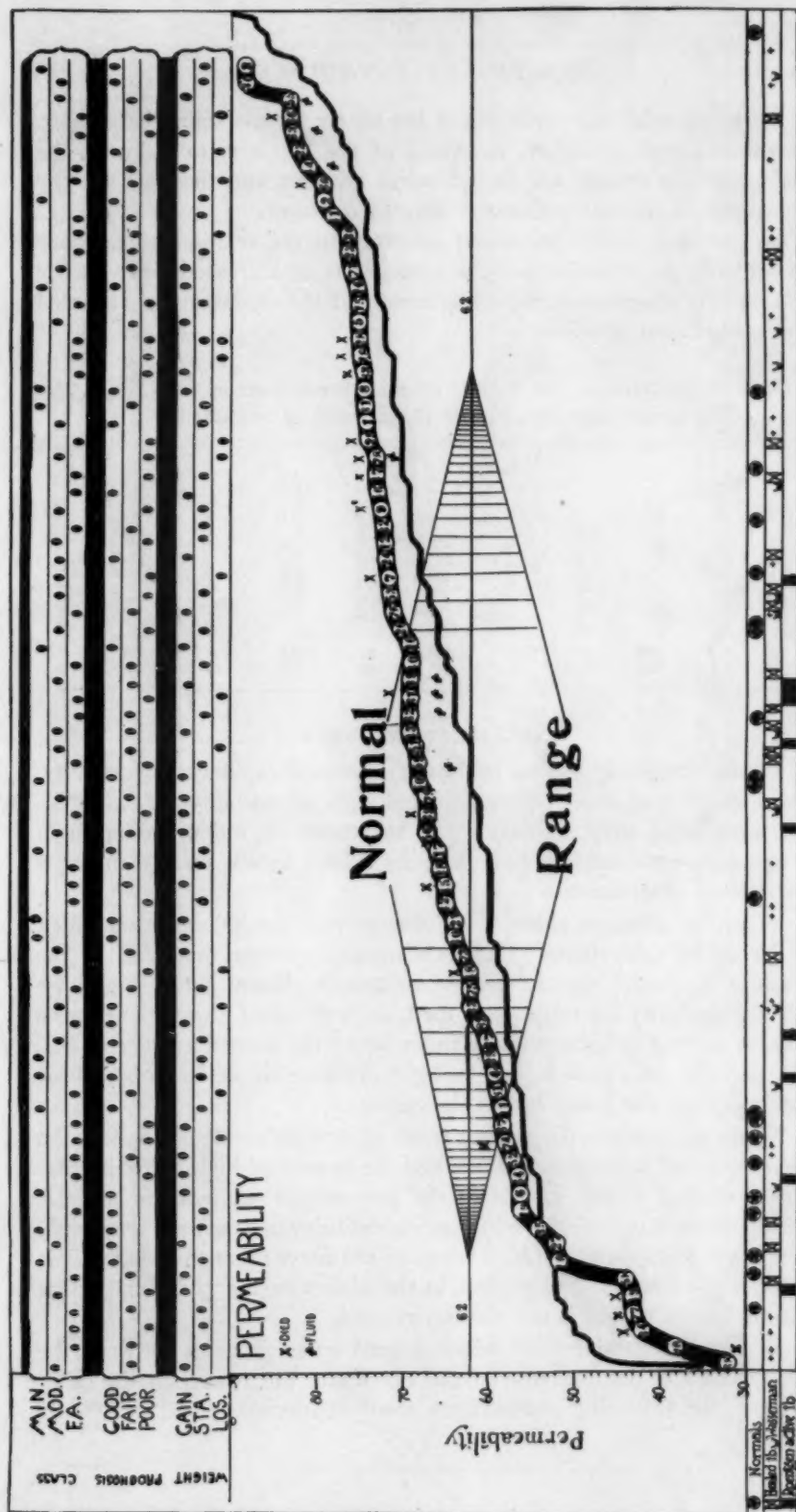


Chart 3.—The curve of capillary permeability in patients with tuberculosis. The chart is explained in the legend for chart 1.

In the group with low permeability the blister time is somewhat longer, the calcium level is higher, the value of the K/Ca ratio is lower, the total protein is greater but the globulins are less, and the time for the absorption of the salt solution is somewhat longer.

In previous papers we called attention to the relation of capillary permeability to tuberculosis—the association of increased permeability with clinical progression, etc. The results of the examinations recorded here confirm our previous work.

TABLE 4.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Permeability of the Capillaries*

Capillary Permeability	Blister Time, Hours	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	Globulin, per Cent of Total Protein	Reaction to Tuberculin at 24 Hours, Mm.	CO ₂ Combining Power	NaCl Solution Absorption, Minutes	Deaths
54	7.7	10.6	19.3	1.8	9.92	25	8.7	55.5	80	7
78	7.1	10.3	20.2	2	8.4	36	8.3	57	70	6

INFLAMMATORY INDEX

In the foregoing studies of blister time and capillary permeability, it was shown that short blister time and high permeability were, in general, associated with activity. The inflammatory index, taking both factors into consideration (permeability/blister time), merely confirms this general observation.

When we examine chart 4, we observe that the inflammatory index of the entire tuberculous group is somewhat greater than that of the group of "normal" persons and miscellaneous clinical patients, and we find the majority of those who died, as well as of the patients with effusion, having an inflammatory index above the normal average of 8.2. The persons who gave roentgenologic evidence of active tuberculosis appear toward the lower end of the curve.

When we analyze the twenty cases of low inflammatory index, the thirty-seven of intermediate index and the twenty of high index in relation to clinical status, we obtain the percentages set forth in table 5. It is apparent that the cases of far advanced tuberculosis more frequently occupy the middle and the high range of the curve; that the prognosis is better at the low end and poorest in the higher region and, finally, that gain or loss in weight is not directly related.

In examining table 6, in which a comparison is made between the twenty cases at one extreme of the curve and the twenty at the other extreme, the following observations seem of interest: The groups do

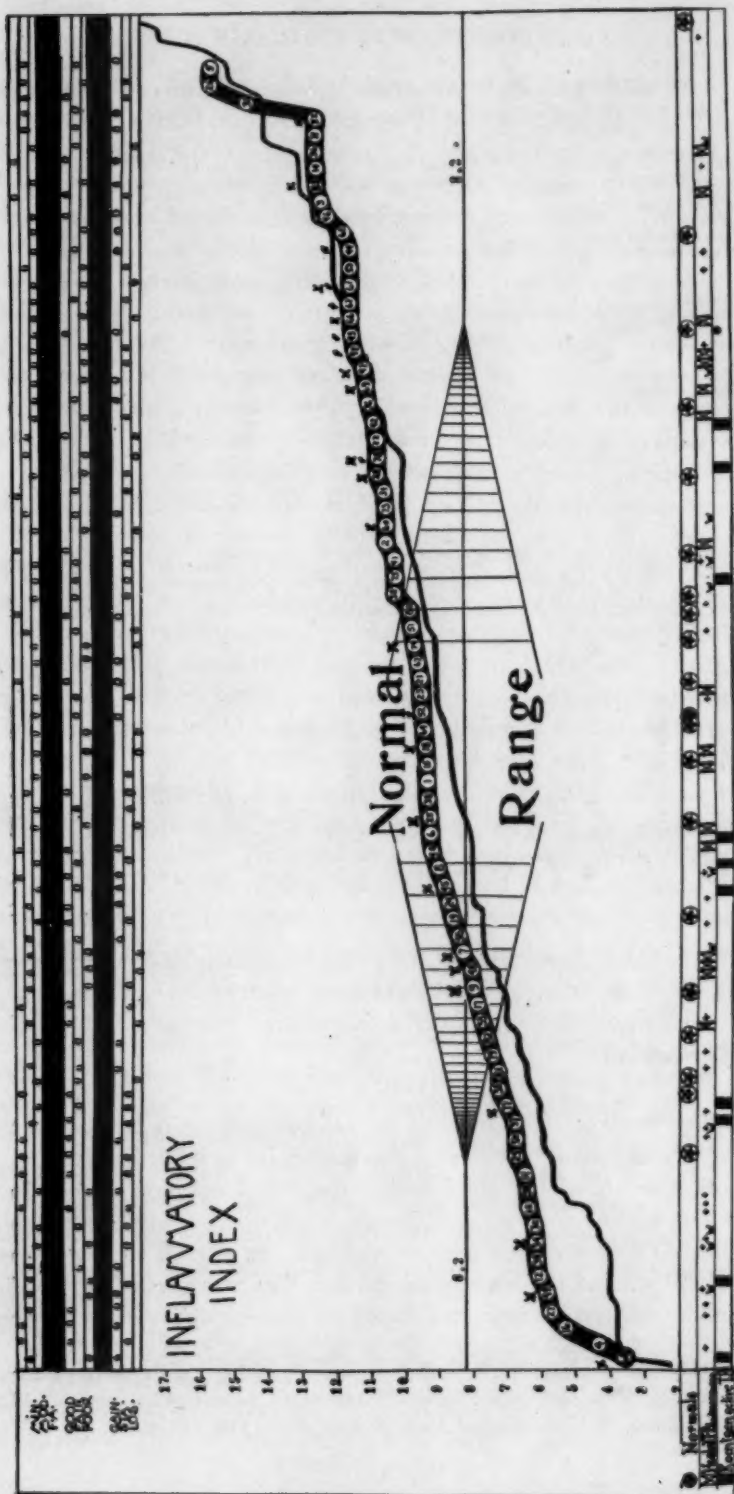


Chart 4.—The curve of the inflationary index.

TABLE 5.—Comparison of the Groups with the Low, the Medium and the High Values of the Inflammatory Index, with Regard to Clinical Status

Clinical Classification of Patients	Low Index (30 Patients)	Medium Index (37 Patients)	High Index (20 Patients)
As to Type of Tuberculosis			
Minimal.....	25%	20%	10%
Moderately advanced.....	37%	30%	30%
Far advanced.....	30%	50%	60%
	100%	100%	100%
As to Prognosis			
Good.....	45%	30%	25%
Fair.....	30%	35%	30%
Poor.....	25%	35%	45%
	100%	100%	100%
As to Weight Curve			
Gaining.....	45%	30%	50%
Stationary.....	50%	40%	35%
Losing.....	5%	30%	15%
	100%	100%	100%

TABLE 6.—Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the Inflammatory Index

Inflammatory Index	Blister Time, Hours	Capillary Permeability	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Globulin, per Cent of Total Protein	Protein, Mg.	Age	Reaction to Epinephrine, Wheel, Mm.	Reaction to Epinephrine, Flare, Mm.	Endothelial Reaction	Daranyi Reaction	Deaths
6.3	8.85	55.69	10.6	19.6	1.85	21.8	9.113	31.6	14.02	5.60	5+ 15—	10+ 8—	6
12.33	5.25	79.9	10.8	19.22	1.78	32.7	8.72	27.6	15.02	6.84	8+ 12—	13+ 6—	6

not differ in blood chemistry, but the group with the high index has more globulin, less protein, greater intracutaneous reactivity to epinephrine and a greater number each of positive endothelial reactions and positive Daranyi reactions.

CALCIUM *

The literature on the subject of the calcium and the potassium of the blood in tuberculosis is extensive. We shall refer to it but briefly.

Voorhoeve³ is of the opinion that the actual calcium balance in a tuberculous patient is of no significance, since decalcification is relative, depending on the amount of calcium supplied. In a small series of cases, he carefully studied the amount of calcium that was needed in the diet to maintain calcium balance and found no striking differences between

* Read before the Section on Pathology and Physiology at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, June 13, 1928.

3. Voorhoeve, N.: *Deutsches Arch. f. klin. Med.* **110**:231, 1913.

tuberculous and nontuberculous subjects. The analysis of Halverson⁴ is interesting in that his determination of the calcium content of the blood of patients with advancing tuberculosis and of those convalescing from tuberculosis revealed that in persons with incipient tuberculosis (of whom those on a milk diet showed marked improvement) the value of the calcium in the serum was normal and fairly constant. In no case was the calcium value increased above the normal by a calcium diet. In patients with advanced tuberculosis the variations were greater, and patients who were improving showed, on the average, slightly higher values than did those who were not improving. No marked deviations from the normal, however, were observed in the calcium content of the serum of patients in the various stages of pulmonary tuberculosis.

A review of the literature on the therapeutic use of calcium in tuberculosis reveals a considerable body of clinical observation indicating an inhibitory effect on the tuberculosis itself, as well as on certain of its complications; a certain amount of evidence that favorable results are not obtainable, and a complete lack of convincing experimental evidence in support of calcium therapy. The hypothesis of a decalcification or demineralization in tuberculosis, according to Maver and Wells,⁵ does not receive support from the most carefully conducted investigations. There is no demonstrable deficiency of calcium in the blood or tissues in tuberculosis, and the feeding of calcium salts does not appreciably increase the amount of calcium in the blood when this is already normal. Experiments conducted by Maver and Wells showed that guinea-pigs on an ordinary laboratory diet exhibited some variations in the calcium content of the same tissue in different animals and of different tissues in the same animals; yet, averaged in a series of animals, the results were not far from identical, being generally lowest for the liver and highest for the lymph nodes, but not far from the content of the blood—that is, from 10 to 13 mg. of calcium for each 100 Gm. moist weight. These studies have failed to produce experimental evidence to support the empirical clinical evidence that the administration of calcium has a healing influence on the course of tuberculous infection.

Determinations of the calcium concentration of the human serum as determined by Barkus⁶ reveal a slightly increased value in the groups with destructive and destructive-proliferative tuberculosis. The values obtained in the group with proliferative disease were normal values and those in the group with atrophic manifestations of the disease were decreased.

4. Halverson, J. O.; Mohler, H. K., and Bergeim, Olaf: Calcium in Blood, *J. A. M. A.* **68**:1309 (May 5) 1917.

5. Maver, M., and Wells, H. G.: *Am. Rev. Tuberc.* **6**:649, 1922.

6. Barkus, O.: *Am. Rev. Tuberc.* **9**:61, 1924.

Observations made by Matz⁷ on the blood of both normal and tuberculous subjects show that there is little variation in the calcium content of the serum. Schoenheit⁸ noted that values for calcium in the blood plasma of normal persons, determined after ashing it, were similar to the values found by others, but that those for the blood plasma of tuberculous patients were considerably less.

According to Greisheimer and Van Winkle,⁹ tuberculosis is not characterized by a demineralization. Patients who regularly drink a liberal amount of milk tend to show higher calcium levels than those who refuse it. The taking of cod liver oil does not markedly increase the calcium in the plasma of tuberculous adults even when there is clinical improvement. There is no constant difference in calcium content as between the sexes; nor is there a constant difference as between ages, although the tendency is toward lower values with increasing age. Examinations were made by Brockbank¹⁰ in seventy cases of pulmonary tuberculosis, and the value of the calcium in the serum was found varying between 8.6 and 12 mg. per hundred cubic centimeters, the normal value being 10 mg. per hundred cubic centimeters of serum. When the cases were graded according to their severity, it was observed that the average amount of calcium in the serum was decreased when the disease was acute, and was increased when the lesions had healed, with proportionate results in the intermediate stages. The difference amounted to 20 per cent. The calcium was not diminished in patients who were coughing up blood, as compared with patients in a similar stage of the disease but without that symptom. It was found that calcium, if given by mouth, failed to alter the level of the serum calcium materially, but when given intravenously it raised the serum content of calcium above the normal for forty-eight hours.

Nearly 100 estimations made by Ellman¹¹ show that the calcium content of the blood in pulmonary tuberculosis is within normal limits (from 9 to 11 mg. per hundred cubic centimeters); but this calcium content can be raised from the minimum to the maximum with corresponding improvement in the patient's general condition by calcium or parathyroid therapy. Krömecke,¹² as well as Rosenstein and Schmidke,¹³ found an increase in the blood calcium in cases of tuberculosis with a favorable prognosis.

7. Matz, P. B.: *Am. Rev. Tuberc.* **11**:250, 1925.

8. Schoenheit, E. W.: *Am. J. M. Sc.* **170**:689, 1925.

9. Greisheimer, E. M., and Van Winkle, C. C.: *Am. Rev. Tuberc.* **15**:270, 1927.

10. Brockbank, W.: *Quart. J. Med.* **20**:431, 1927.

11. Ellman, P.: *Tubercle* **9**:162, 1928.

12. Krömecke, Franz: *Beitr. z. Klin. d. Tuberc.* **57**:467, 1924.

13. Rosenstein and Schmidke: *Beitr. z. Klin. d. Tuberc.* **50**:199, 1924.

When our patients are grouped on the basis of the classifications of the National Tuberculosis Association, the relation of clinical status to calcium and potassium values is not clear (table 7). It will be seen that our group with minimal A disease has the highest value of the K/Ca ratio and all the more advanced cases far lower values, but there is no progression or regularity.

TABLE 7.—*Comparison of the Calcium Levels and of the Potassium Levels of the Blood of Tuberculous Patients Grouped on the Basis of the Classifications of the N. T. A.*

Group, Classified as to Tuberculosis	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Minimal A.....	9.1	20.8	2.27
Minimal B.....	10.7	18.5	1.73
Moderately advanced A.....	10.8	17.1	1.6
Moderately advanced B.....	10.2	19.6	1.92
Far advanced A.....	9.8	19	1.93
Far advanced B.....	10.5	19.8	1.87
Far advanced C.....	10.5	18.4	1.75

TABLE 8.—*Comparison of the Calcium Levels and of the Potassium Levels of the Blood of Tuberculous Patients Grouped According to the Weight Curve*

Group, Classified as to Weight Curve	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Gaining.....	10.6	18.9	1.8
Stationary.....	10.4	20.1	1.96
Losing.....	10.2	17.7	1.73

TABLE 9.—*Comparison of the Calcium Levels and Potassium Levels of the Blood of Tuberculous Patients Grouped on the Basis of Prognosis*

Group, Classified as to Prognosis	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Gaining—continued to gain.....	10.7	18.5	1.75
Gaining—later declined.....	10.6	18.6	1.77
Stationary.....	9.1	19.8	1.97
Losing—later gained.....	9.8	21	2.17
Losing—continued to decline.....	10.2	18.1	1.79

When the patients are classified in accordance with the weight curve, the values for the groups are as recorded in table 8. Here we have a definite reduction of the calcium as we pass from the gaining to the losing group, the losing group giving the lowest value of the K/Ca ratio.

Finally, in table 9, we present the results when the grouping is made on the basis of prognosis. It is obvious that the groups who were gaining had the highest calcium levels but the high level in the last group may seem confusing. We are of the impression that the two groups present totally different pictures of calcium metabolism despite the similarity of the determinations. In the groups of patients who are gaining we have the organism maintaining a high calcium level as part of the picture of resistance, and this without loss from the body—such patients are, as a rule, in calcium balance. In the group of patients who are losing we have

a fairly high calcium level, but it represents calcium leaving the tissue and passing out from the body—these patients usually show a negative calcium balance.

The three intermediate groups seem to bear out this assumption, the stationary group having the lowest amount. Certainly, the calcium values seem of greater importance than the potassium values or the values of the K/Ca ratios in all the clinical correlations.

These assumptions seem to be made more probable when we recall the calcium values of the blood of the so-called "normal" groups

TABLE 10.—*Comparison of the Calcium Levels and the Potassium Levels of the Blood of the "Normal" Groups*

Clinical Group	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Truly normal.....	9.7	20.3	2.1
Having healed tuberculosis (Roentgen).....	10.5	20.8	1.98
Having active tuberculosis (Roentgen)*....	9.6	20.1	2.08

* Silent lesions, probably chronic.

TABLE 11.—*Comparison of the Groups with the Low, the Medium and the High Calcium Levels, with Regard to Clinical Status*

Clinical Classification of Patients	Low Calcium (20 Patients)	Medium Calcium (35 Patients)	High Calcium (20 Patients)
As to Type of Tuberculosis			
Minimal.....	25%	20%	25%
Moderately advanced.....	35%	25%	45%
Far advanced.....	40%	55%	30%
	100%	100%	100%
As to Prognosis			
Good.....	40%	37%	38%
Fair.....	35%	20%	40%
Poor.....	25%	43%	25%
	100%	100%	100%
As to Weight Curve			
Gaining.....	45%	28%	55%
Stationary.....	35%	40%	45%
Losing.....	20%	32%	0
	100%	100%	100%

(table 10). Here, again, the high calcium level occurs in the healed (resistant) group; the group with only roentgen evidence of activity (chronic tuberculosis) has a low level.

We turn now to an analysis of the determinations made for the group and arranged in curves from low to high levels.

The range of calcium values for the series is from a low of 8.2 to a high of 13.4, and it is at once apparent, on inspection of chart 5, that a considerable number of the patients at the low end of the curve have died, while the patients with pleural effusion are scattered to a greater extent.

The distribution of the clinical types on the curve is shown in table 11. The most striking feature is the fact that none of the twenty patients at

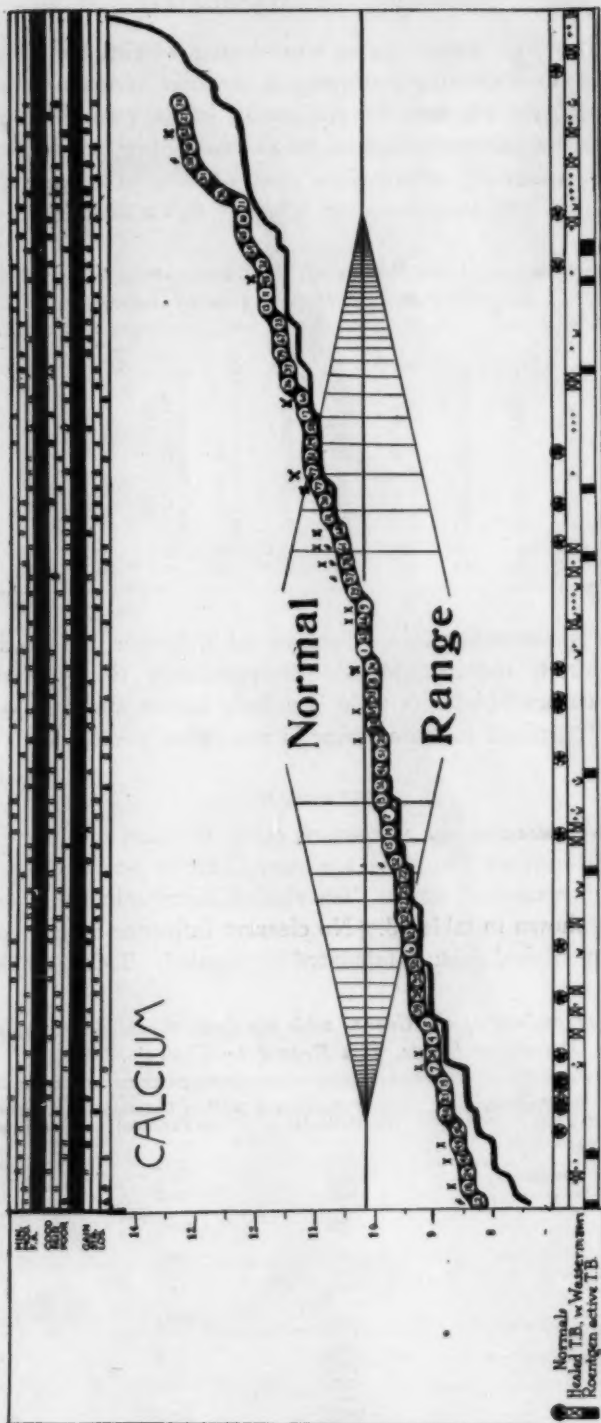


Chart 5.—The calcium curve.

the high end of the calcium curve were losing weight, the entire group either gaining or remaining stationary at the time of examination.

In table 12, the averages for the results of the examinations of the patients with the extremely high or the extremely low calcium values are shown. The following observations seem of interest: The group with the low calcium level has, of course, a higher K/Ca ratio; the inflamma-

TABLE 12.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Calcium Levels*

Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Blister Time, Hours	Inflammatory Index	Globulin, per Cent of Total Protein	Protein, Mg.	CO ₂ Combining Power	Reaction to Thyroxin, Flare, Min.	NaCl Disappearance Time (McClure-Aldrich), Min.	Corpuscles/Plasma Ratio	Reaction to Epinephrine, Vagotonic	Reaction to Epinephrine, Sympathetico-tonic	Deaths
8.98	19.4	2.17	8	8.46	27	8.42	55.4	3.8	89.1	41	17	5	6
12.1	19.8	1.62	6.9	9.5	34.2	9.08	57.3	12.97	65.7	39.6	12	3	5

tory index is somewhat lower because of a longer blister time, the McClure-Aldrich sodium chloride disappearance time is somewhat longer, the corpuscle/plasma ratio is a little higher and the number of "vagotonic" reactions to epinephrine is somewhat greater.

POTASSIUM

When we examine the potassium curve in chart 6, the relation to deaths would indicate that these are more likely to occur in the patients with the high potassium range. The clinical distribution of the cases on the curve is shown in table 13. No clearcut influence of the potassium levels on any clinical feature tabulated is revealed. This is evident, too,

TABLE 13.—*Comparison of the Groups with the Low, the Medium and the High Potassium Levels, with Regard to Clinical Status*

Clinical Classification of Patients	Low Potassium (20 Patients)	Medium Potassium (35 Patients)	High Potassium (20 Patients)
As to Type of Tuberculosis			
Minimal.....	20%	23%	30%
Moderately advanced.....	45%	28%	25%
Far advanced.....	35%	49%	45%
	100%	100%	100%
As to Prognosis			
Good.....	40%	28%	50%
Fair.....	30%	28%	30%
Poor.....	30%	44%	20%
	100%	100%	100%
As to Weight Curve			
Gaining.....	40%	51%	25%
Stationary.....	35%	31%	60%
Losing.....	25%	18%	15%
	100%	100%	100%

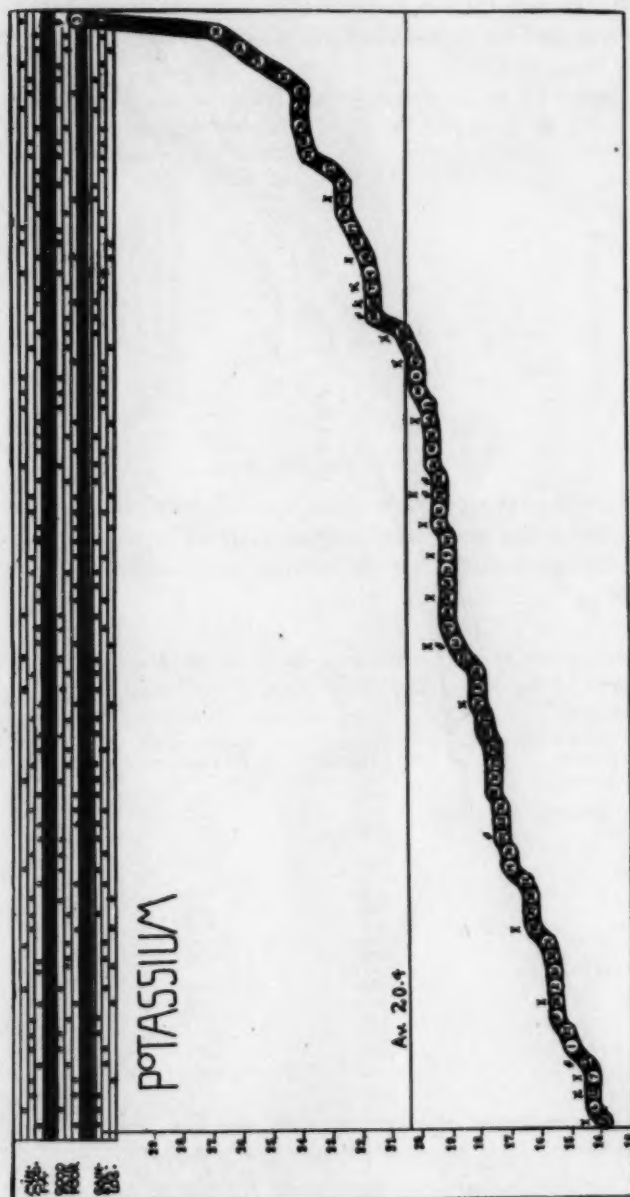


Chart 6.—The potassium curve.

when we inspect the averages of the other determinations for the two extreme groups (table 14). The only fact of apparent interest is the greater size of the reactions to thyroxin in the group with the low level of potassium. In part 1, table 1, the relation between the reactions of the skin to thyroxin and the potassium level is made evident.

TABLE 14.—*Comparison of the Results of the Examinations of the Groups with the Low and the High Potassium Levels*

Potassium, Mg. per 100 Cc.	Calcium, Mg.	K/Ca Ratio	Age	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Corpuscles/Plasma Ratio	Deaths
15.5	10	1.56	28.8	9.6	3.35	40.7	5
23.7	10.2	2.37	33.8	8.4	2.55	38.1	6

THE K/CA RATIO

The K/Ca ratio has apparently much less influence on the tuberculous process than the actual amount of calcium. In the curve in chart 7, the deaths are well distributed along the various levels, as are the cases with pleural effusion.

TABLE 15.—*Comparison of the Groups with the Low, the Medium and the High Values of the K/Ca Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Ratio (20 Patients)	Medium Ratio (35 Patients)	High Ratio (20 Patients)
As to Type of Tuberculosis			
Minimal.....	25%	60%	20%
Moderately advanced.....	45%	28%	25%
Far advanced.....	30%	52%	45%
	100%	100%	100%
As to Prognosis			
Good.....	35%	31%	50%
Fair.....	30%	23%	35%
Poor.....	35%	44%	15%
	100%	100%	100%
As to Weight Curve			
Gaining.....	55%	34%	25%
Stationary.....	30%	43%	45%
Losing.....	15%	23%	25%
	100%	100%	100%

The clinical status of the groups with the low, medium and high values of the K/Ca ratio is made evident in the percentages recorded in table 15. The only apparently significant feature is that with a high value of the ratio the prognosis is apparently better.

The averages for various determinations in the examination of the extreme groups show no striking differences (table 16). The group

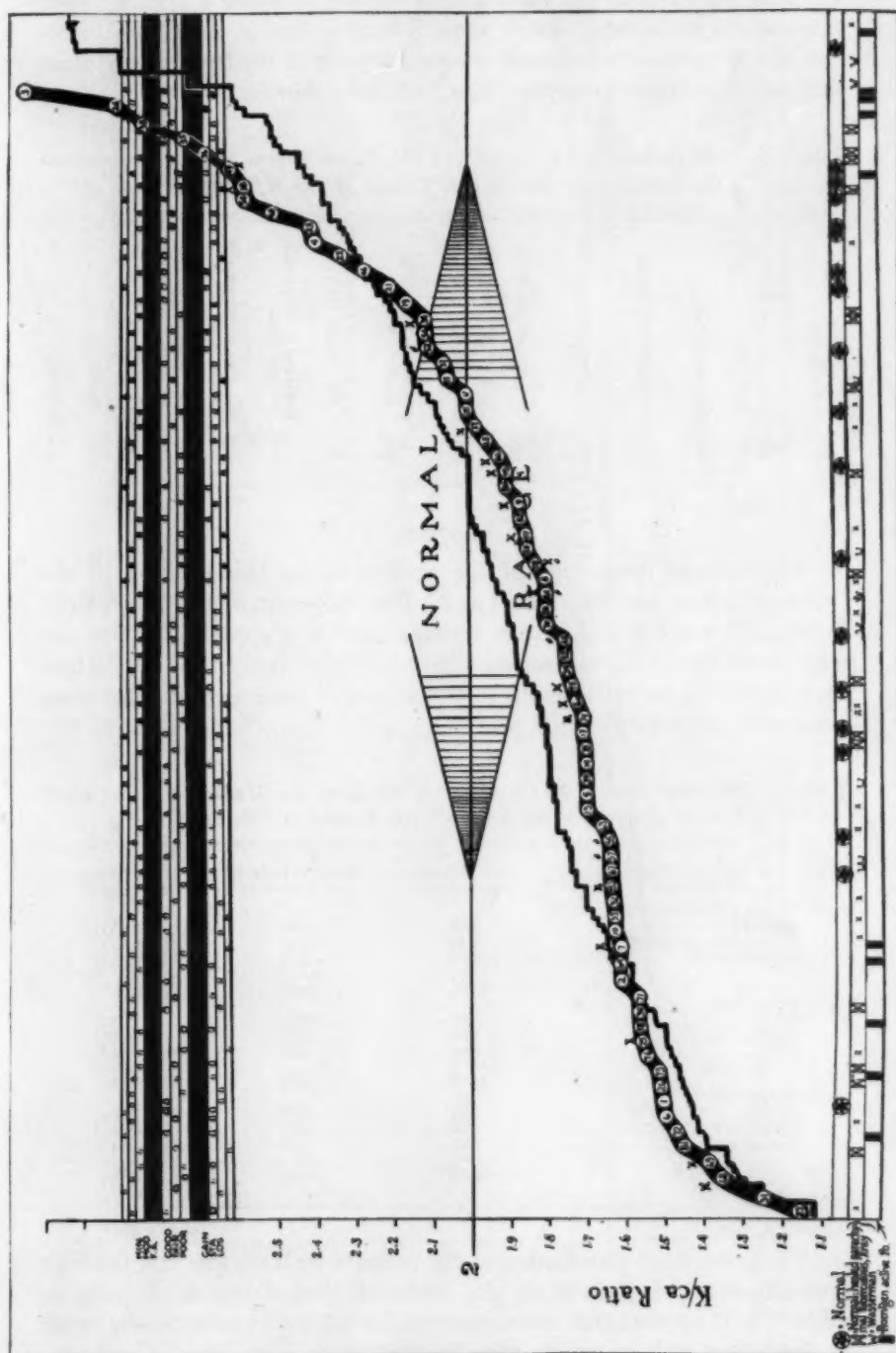


Chart 7.—The curve of the K/Ca ratio.

with the low value of the ratio weighs slightly less, has a slightly lower value of the cholesterol lecithin ratio, a smaller flare at the site of injection of epinephrine and a larger wheal at the site of injection of thyroxin, and the salt solution resorption time is a little shorter.

TABLE 16.—Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the K/Ca Ratio

K/Ca Ratio	Calcium, Mg. per 100 Cc.	Potassium, Mg.	Inflammatory Index	Pulse Pressure	Weight/Length Ratio	Lecithin, Mg.	Cholesterol/Lecithin Ratio	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	NaCl Resorption (McClure-Aldrich) Time, Minutes	Corpuscles/Plasma Ratio	Deaths
1.40	11.1	16.5	9.3	45.6	1.91	173.5	1.16	6.16	9.05	3.4	71.6	38.1	0
2.44	9.29	22.6	8.79	51.4	2.06	156	1.26	7.50	8.3	3.85	84.7	40	4

PROTEIN

The average percentage of the protein in the blood serum of the "normal" group was determined as 8. For the serum of our tuberculous group, this was 8.8, and, as one surveys chart 8, it appears that patients with more advanced tuberculosis have a higher concentration. Thus, there appear to be more deaths in this region of the curve and also more cases with pleural effusion.

TABLE 17.—Comparison of the Groups with the Low, the Medium and the High Levels of Protein in the Serum, with Regard to Clinical Status

Clinical Classification of Patients	Low Protein (20 Patients)	Medium Protein (41 Patients)	High Protein (20 Patients)
As to Type of Tuberculosis			
Minimal.....	35%	22%	10%
Moderately advanced.....	40%	29%	25%
Far advanced.....	25%	52%	65%
	100%	100%	100%
As to Prognosis			
Good.....	60%	39%	15%
Fair.....	30%	29%	40%
Poor.....	10%	38%	45%
	100%	100%	100%
As to Weight Curve			
Gaining.....	45%	34%	55%
Stationary.....	40%	53%	15%
Losing.....	15%	13%	30%
	100%	100%	100%

The percentage distribution of the patients with the low and the high concentrations of protein on the basis of clinical status is given in table 17. It appears that more cases of far advanced tuberculosis occur at the upper end, at which, also, the prognosis is poorest. Curiously,

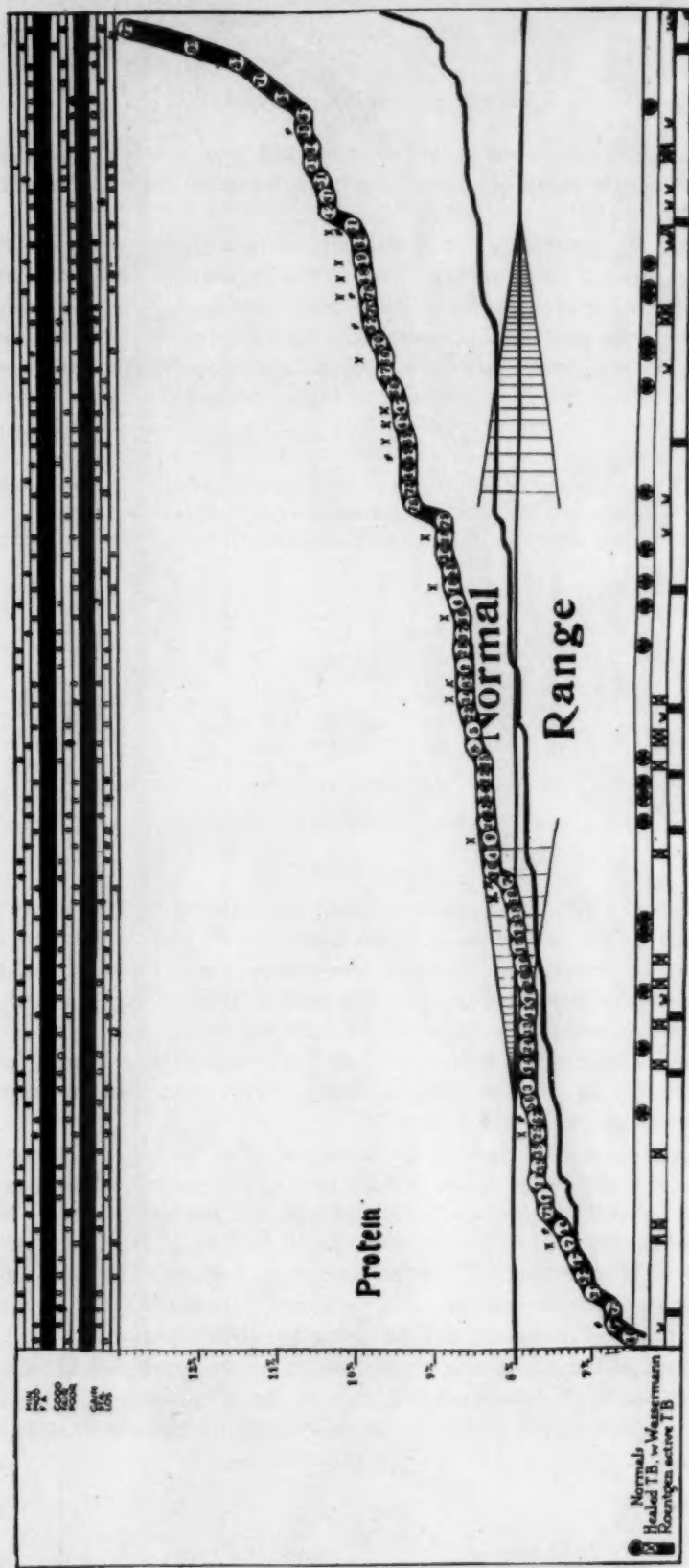


Chart 8.—The protein curve.

both gain and loss in weight are most marked here, reflecting, probably, the fact that in many instances these gains represent fluctuations in the water balance.

Table 18, presenting the results of the examinations of the two extreme groups, offers a number of contrasts, some of which are contradictory. The group with the low protein has less globulin, fewer positive tuberculin and Daranyi reactions, a higher value of the corpuscles/plasma ratio, a greater number of sympathetotonic vascular reactions, a longer blister time, but a somewhat higher permeability, and a higher value of the K/Ca ratio.

TABLE 18.—*Comparison of the Results of the Examinations of the Groups Having the Lowest and the Highest Concentrations of Protein in the Serum*

Protein, Mg. per 100 Cc.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Albumin	Globulin, per Cent of Total Protein	Reaction to Tuberculin, Mm.	Daranyi Reaction	Corpuscles/Plasma Ratio	Reaction to Epinephrine	Deaths
7.454	7.6	70.5	9.5	9.79	19.4	2	77.2	22.8	9+	11+	40.7	9V 118	12
10.526	6.8	61.9	9.07	10.71	19	1.77	80.2	39.8	14+	16+	37.7	13V 78	7

GLOBULINS

There can be little doubt concerning the relation of the increase in globulins to the prognosis in tuberculosis. With this increase in the globulins in cases of far advanced tuberculosis, are to be associated the changes in the sedimentation time, the increase in fibrinogen, the various flocculations, which depend on the colloidal instability, etc.

When we examine the curve in chart 9, it is immediately apparent that the high end has the majority of deaths. The cases showing pleural exudations are equally distributed.

The percentage analysis of the cases plotted on the curve with regard to clinical condition is shown in table 19. The majority of the cases of far advanced tuberculosis occur at the high end and the prognosis here is poorest. On the other hand, the relation of gain or loss of weight to the curve is uncertain. While, of course, in the low end of the curve a majority of the patients are gaining or are stationary, in the high end the gaining, the stationary and the losing are about equally divided. As mentioned in the corresponding discussion of the total protein, this is probably to be explained on the basis of the fluctuation of the water balance, which occurs so readily in these cases of far advanced tuberculosis.

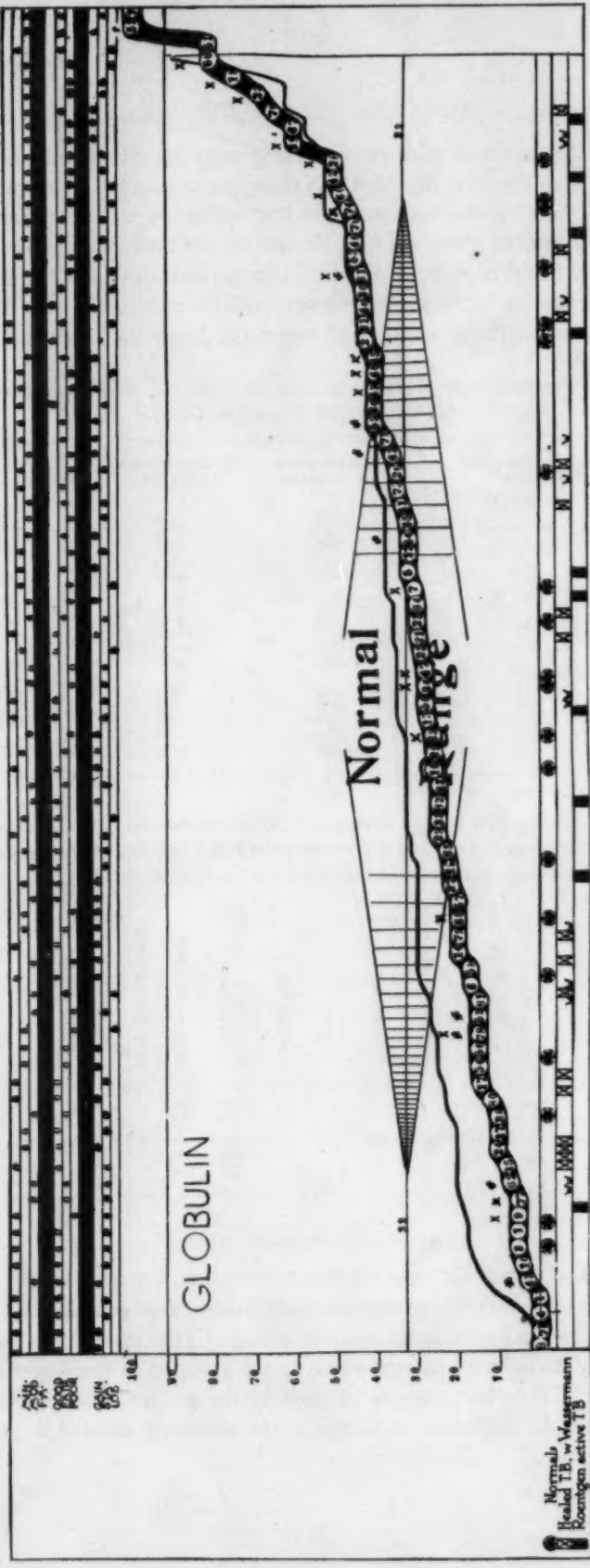


Chart 9.—The globulin curve.

Table 20, in which the two extreme groups are compared, shows the following conditions, many of which correspond with the observations in the groups having the high and the low values of total protein: The group with the low globulins has a longer blister time, a lower inflammatory index, a higher value of the K/Ca ratio, less protein, a higher value of the corpuscles/plasma ratio, fewer positive tuberculin and Daranyi reactions and a greater number of vagotonic reactions to epinephrine.

TABLE 19.—*Comparison of the Groups with the Low, the Medium and the High Levels of Globulins, with Regard to Clinical Status*

Clinical Classification of Patients	Low Globulins (20 Patients)	Medium Globulins (42 Patients)	High Globulins (20 Patients)
As to Type of Tuberculosis			
Minimal.....	55%	19%	5%
Moderately advanced.....	25%	40%	10%
Far advanced.....	20%	41%	85%
	100%	100%	100%
As to Prognosis			
Good.....	65%	38%	5%
Fair.....	25%	28%	40%
Poor.....	10%	34%	55%
	100%	100%	100%
As to Weight Curve			
Gaining.....	35%	50%	30%
Stationary.....	60%	38%	35%
Losing.....	5%	12%	35%
	100%	100%	100%

TABLE 20.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Concentrations of Globulins in the Serum*

Globulins, Mg. per 100 Gc.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Albumin	Protein, Mg.	Tuberculous Complement Fixation	Daranyi Reaction	Corpuscles/Plasma Ratio	Diagnosis	Reaction to Epinephrine	Deaths
7.2	7.0	65.8	8.6	10.1	20.7	2.07	92.8	8.18	13+ Neg. 0+	12+ Neg. 8+	4.16	9 minimal 7 mod. ad. 4 far ad.	13V 78	3
50.3	6.62	68.1	10.3	10.5	19.6	1.88	40.7	9.37	3— Neg. 17+	1— Neg. 18+	39.1	1 minimal 2 mod. ad. 17 far ad.	6V 148	10

BASAL METABOLIC RATE

The basal metabolic rate for the tuberculous group averages $+6.5$, and the curve (chart 10) proportionately follows that established for our "normal" and miscellaneous clinical group. The fatal cases and the majority of those with pleural effusion are grouped at the upper end of the curve. The clinical status of each of the groups with the low, the medium and the high rates is shown in the percentages listed in table 21.

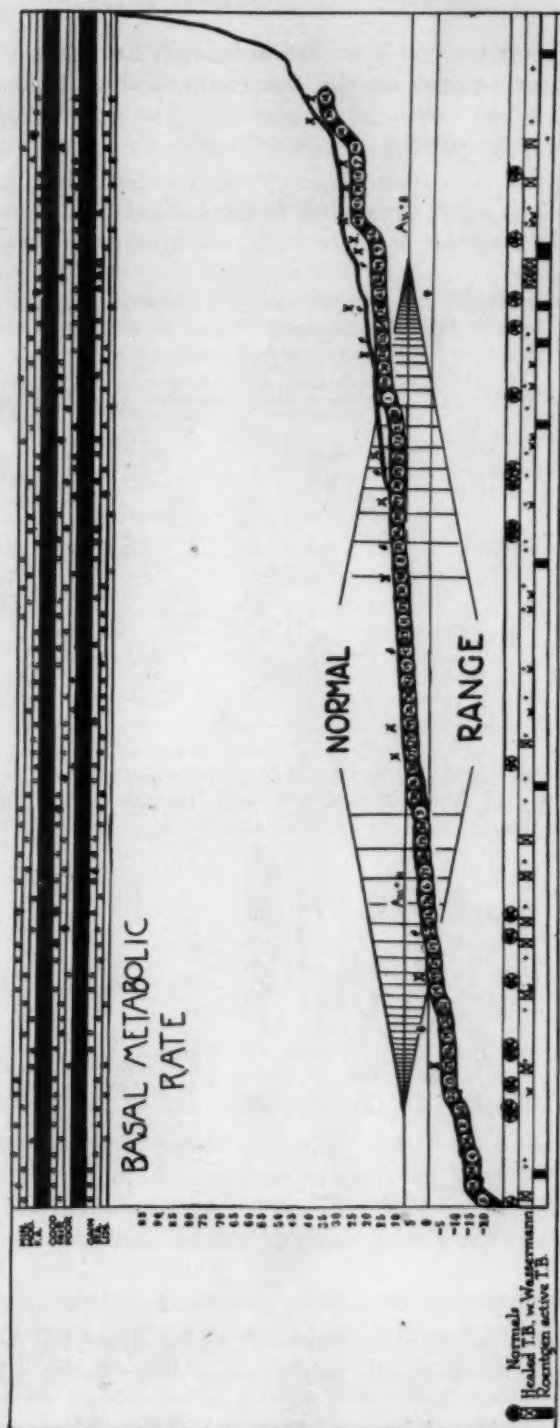


Chart 10.—The curve of the basal metabolic rate.

In the group with the low basal metabolic rate, the cases of minimal manifestation predominate; in the group with the high basal metabolic rate, the cases of far advanced tuberculosis. The same ratios are true for the good and the poor prognoses. There is no apparent relation to the weight curve.

In table 22, in which the groups at the ends of the curve are compared in detail, the group with the high rate is shown to have a some-

TABLE 21.—*Comparison of the Groups Having, Respectively, Low, Medium and High Basal Metabolic Rates, with Regard to Clinical Status*

Clinical Classification of Patients	Low Basal Metabolic Rate (20 Patients)	Medium Basal Metabolic Rate (35 Patients)	High Basal Metabolic Rate (20 Patients)
As to Type of Tuberculosis			
Minimal.....	45%	23%	10%
Moderately advanced.....	30%	31%	30%
Far advanced.....	25%	46%	60%
	100%	100%	100%
As to Prognosis			
Good.....	60%	40%	20%
Fair.....	30%	37%	15%
Poor.....	10%	23%	65%
	100%	100%	100%
As to Weight Curve			
Gaining.....	40%	43%	33%
Stationary.....	40%	48%	40%
Losing.....	20%	9%	27%
	100%	100%	100%

TABLE 22.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Basal Metabolic Rates*

Basal Metabolic Rate	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Min.	CO ₂ Combining Power	Ice Reaction Time, Seconds	Reaction to Epinephrine, Wheal, Min.	Reaction to Epinephrine, Flare, Min.	Diagnosis	Prognosis	NaCl Solution Resorption Time, Minutes	Deaths
- 8.6	9.8	19.6	2	95.9	55.7	13.3	14.36	6.21	8 minimal 7 mod. advanced 5 far advanced	12 good 6 fair 2 poor	80.8	3
+21.3	10.3	19.3	1.87	71	57.2	9.3	16.37	6.93	2 minimal 6 mod. advanced 12 far advanced	4 good 8 fair 13 poor	60	11

what lower value of the K/Ca ratio, a shorter Kromayer light erythema time and a shorter ice reaction time and a larger flare on the injection of epinephrine.

VASCULAR REACTIONS TO EPINEPHRINE

In two papers previously published,¹⁴ we described the reactions of our tuberculous group to the subcutaneous injection of epinephrine.

14. Petersen, W. F., and Levinson, S. A.: *Am. Rev. Tuberc.* **18**:616, 1928. Hillebrand and De Trana: *Ibid.* **18**:626, 1928.

Both the individual curves and their analysis on the basis of clinical status, as well as composite curves, were presented in detail.

CO₂ COMBINING POWER

We might expect that the CO₂ combining power of the patient would show relatively little concurrence with the clinical activity. In chart 11,

TABLE 23.—Comparison of the Groups with the Low, the Medium and the High CO₂ Combining Power, with Regard to Clinical Status

Clinical Classification of Patients	Low CO ₂ Combining Power (20 Patients)	Medium CO ₂ Combining Power (39 Patients)	High CO ₂ Combining Power (20 Patients)
As to Type of Tuberculosis			
Minimal.....	30%	25%	5%
Moderately advanced.....	10%	39%	45%
Far advanced.....	60%	36%	50%
	100%	100%	100%
As to Prognosis			
Good.....	40%	41%	20%
Fair.....	30%	23%	40%
Poor.....	30%	34%	40%
	100%	100%	100%
As to Weight Curve			
Gaining.....	35%	44%	45%
Stationary.....	45%	38%	30%
Losing.....	20%	18%	25%
	100%	100%	100%

TABLE 24.—Comparison of the Results of the Examinations of the Groups Having the Lowest and the Highest CO₂ Combining Power

CO ₂ Combining Power	Calcium, Mg.	Potassium, Mg.	K/Oa Ratio	Kromayer Light Erythema Time, Min.	Ice Reaction Time, Seconds	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Flare, Mm.	Corpuscles/Plasma Ratio	Paranyl Reaction	Deaths
49.16	10.3	18.9	1.84	103	13.6	6.24	1.32	40.75	11+	5
63.18	10.90	17.9	1.74	83.1	9.4	7.17	3.4	38.2	18+	5

our strictly normal material is scattered over the entire range of the normal curve, while the cases in which there is roentgen evidence of active tuberculosis tend toward the upper end. The curve for our tuberculous material indicates that deaths, as well as pleural effusion are scattered.

The general clinical status of the patients represented on the curve also indicates that there is no significant difference clinically between the extremes (table 23).

Table 24, in which the groups with the extremely high and the extremely low CO₂ combining power are compared, shows the following

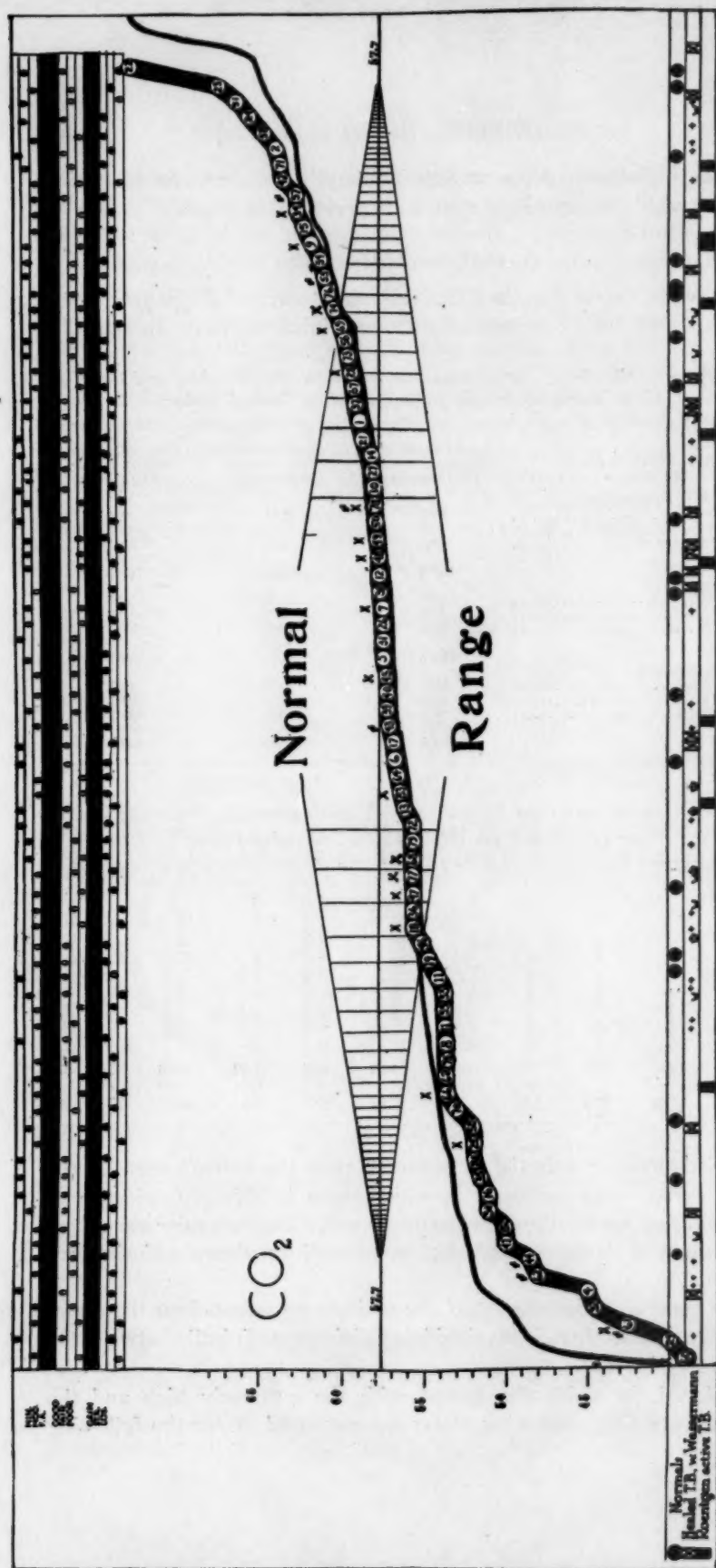


Chart 11.—The curve of the CO_2 combining power.

differences between the groups: The group with the low CO_2 combining power has a higher level of potassium and a higher value of the K/Ca ratio, a longer Kromayer light erythema time, a longer ice reaction time, a smaller flare at the site of the intracutaneous injection of epinephrine and thyroxin and fewer positive Daranyi reactions.

CHOLESTEROL

The association of high cholesterol values with more favorable types of tuberculous infection has been repeatedly suggested. In chart 12, our values for the series of tuberculous patients are considerably lower than those for the "normal" persons and persons with miscellaneous clinical conditions. If it is permissible to draw conclusions from the limited material, it appears, too, that the cases of healed tuberculosis among our "normal" and miscellaneous groups are more apt to be associated with high cholesterol values.

TABLE 25.—Comparison of the Groups with the Low, the Medium and the High Cholesterol Content in the Blood, with Regard to Clinical Status

Clinical Classification of Patients	Low Cholesterol (20 Patients)	Medium Cholesterol (38 Patients)	High Cholesterol (20 Patients)
As to Type of Tuberculosis			
Minimal.....	15%	28%	30%
Moderately advanced.....	15%	37%	40%
Far advanced.....	70%	40%	40%
	100%	100%	100%
As to Prognosis			
Good.....	30%	37%	35%
Fair.....	20%	30%	45%
Poor.....	50%	33%	20%
	100%	100%	100%
As to Weight Curve			
Gaining.....	30%	44%	45%
Stationary.....	50%	37%	45%
Losing.....	20%	19%	10%
	100%	100%	100%

TABLE 26.—Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of Cholesterol in the Serum

Cholesterol, Mg. per 100 Cc.	Diagnosis	Blood Pressure	Globulin, per Cent	Protein, Mg.	Reaction to Epineph- rine, Wheal, Mm.	Reaction to Tubercu- lin, Mm.	Daranyi Reaction	Deaths
157.7	3 minimal 3 moderately advanced 14 far advanced	100.1	39.2	8.365	15.37	8.6	15+ 1—	10
235.1	4 minimal 8 moderately advanced 8 far advanced	123.7	30.0	8.963	14.41	11.1	12+ 5—	8

It is rather striking that so many fatal cases are at the lower end of the curve; the cases with effusion appear more frequently at the opposite end.

The clinical status of the groups with the low, the medium and the high cholesterol values is shown in the percentages set forth in table 25. The group with the lowest cholesterol values contains more cases of far advanced tuberculosis with poor prognosis; many of the patients in this group, however, are either stationary or gaining in weight. The group with the highest cholesterol values contains a greater number of cases of moderately or far advanced tuberculosis; the majority of the patients in this group have a fair or good prognosis and are either stationary or gaining in weight.

Table 25, in which the twenty patients at the low end of the curve are compared with the twenty at the high end, indicates that the low group has a lower blood pressure, more globulin and a smaller reaction to tuberculin. The low group also is characterized by ten fatal cases, as compared with three in the high group.

LECITHIN

An analysis of the lecithin curve in chart 13 from the point of view of the clinical status of the patients represented in it reveals a clinical distribution as tabulated in table 27. The group at the low end of the curve shows the cases of far advanced tuberculosis to be in the majority, with poor or, at best, fair prognosis. The high group, on the other hand, shows more cases of minimal tuberculosis and more with a good prognosis. The relation of these groups to the weight curve is uncertain.

TABLE 27.—*Comparison of the Groups with the Low, the Medium and the High Lecithin Values, with Regard to Clinical Status*

Clinical Classification of Patients	Low Lecithin (20 Patients)	Medium Lecithin (30 Patients)	High Lecithin (20 Patients)
As to Type of Tuberculosis			
Minimal.....	10%	20%	40%
Moderately advanced.....	35%	27%	30%
Far advanced.....	55%	53%	30%
	100%	100%	100%
As to Prognosis			
Good.....	15%	38%	55%
Fair.....	40%	30%	15%
Poor.....	45%	32%	30%
	100%	100%	100%
As to Weight Curve			
Gaining.....	40%	50%	25%
Stationary.....	40%	33%	60%
Losing.....	20%	17%	15%
	100%	100%	100%

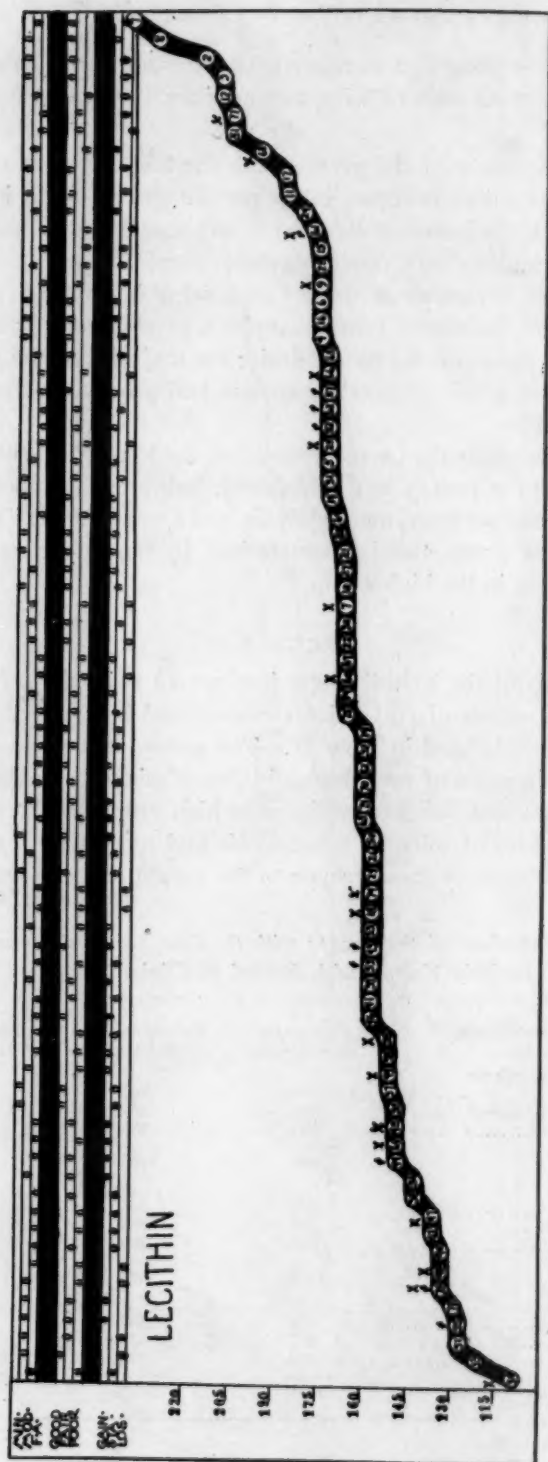


Chart 13.—The lecithin curve.

The table in which the groups at the extreme ends of the curve are compared (table 28) shows the following: The low group has a shorter blister time, higher globulin, a longer Kromayer light erythema time, a larger flare at the site of the injection of epinephrine, as well as a larger reaction to thyroxin and a greater number of positive tuberculin and Daranyi reactions.

TABLE 28.—Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Lecithin Values of the Serum

Lecithin, Mg. per 100 Cc.	Cholesterol/Lecithin Ratio	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Globulin, per Cent of Total Protein	Protein, Mg.	Kromayer Light Erythema Time, Min.	Reaction to Epinephrine, Wheel, Min.	Reaction to Epinephrine, Flare, Min.	Reaction to Thyroxin, Wheel, Min.	Reaction to Thyroxin, Flare, Min.	Weight/Length Ratio	Reaction to Tuberculin, Flare, Min.	Daranyi Reaction	Deaths
138	1.40	7.21	64.4	8.06	10	19.3	1.94	22.6	9.049	84	15.07	7.91	9.45	5.57	1.9	14+	14+	8
191	1.084	8.5	67.1	8.2	10.2	19.3	1.95	24	8.75	67.8	15	5.46	8.3	1.8	1.92	7+	11+	6
																12-	9-	

CHOLESTEROL/LECITHIN RATIO

Since high cholesterol and low lecithin values presumably have some prognostic significance, we have studied this ratio as it involves our material. It is apparent from a survey of the curve in chart 14 that deaths are scattered over the entire range. Here again, cases with effusion are seemingly more common with the high values.

The relation of the ratio to the clinical status of the patient as indicated in table 29 is not clear. There are more cases of moderately advanced and far advanced tuberculosis at the high end of the curve;

TABLE 29.—Comparison of the Groups with the Lowest and the Highest Values of the Cholesterol/Lecithin Ratio, with Regard to Clinical Status

Clinical Classification of Patients	Low Value (30 Patients)	Medium Value (36 Patients)	High Value (20 Patients)
As to Type of Tuberculosis			
Minimal.....	45%	14%	10%
Moderately advanced.....	15%	40%	40%
Far advanced.....	40%	46%	50%
	100%	100%	100%
As to Prognosis			
Good.....	60%	33%	20%
Fair.....	15%	22%	55%
Poor.....	25%	45%	25%
	100%	100%	100%
As to Weight Curve			
Gaining.....	35%	25%	50%
Stationary.....	55%	44%	30%
Losing.....	10%	21%	20%
	100%	100%	100%

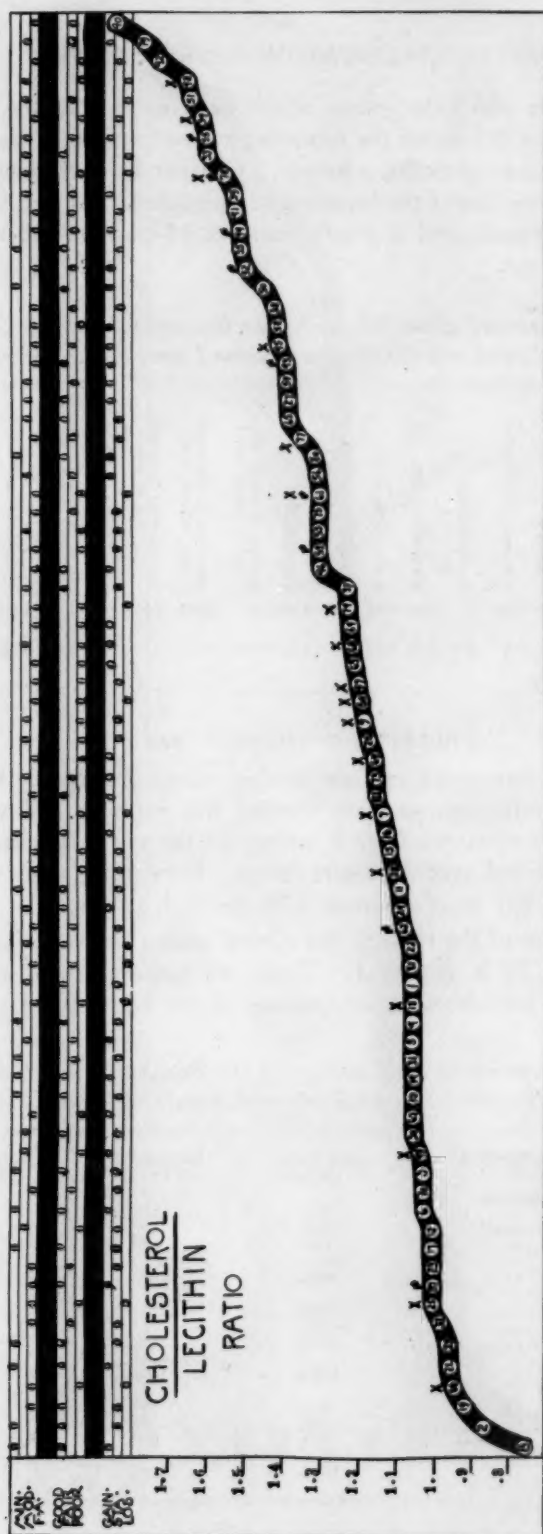


Chart 14.—The curve of the cholesterol/lecithin ratio.

the majority of the patients with the high values are gaining and have a fair prognosis. On the other hand, in the low group there are more cases of minimal manifestation of the disease. The group has more patients with good prognosis (60 per cent) and a far greater number (90 per cent) who are either gaining or stationary. It is evident that the index is of prognostic value only when we take into consideration the stage of the tuberculous process.

As there are no apparent correlations with the results of the other tests, the tables have been omitted. It may be recalled that determinations of cholesterol in our group of 100 "normal" men showed few correlations with other determinations (table 1, part 1).

NONSPECIFIC LEUKOCYTIC REACTION TO AOLAN

When a bland protein is intracutaneously injected, a peripheral vascular constriction takes place, with a coincident leukopenia. At the same time, a splanchnic dilatation apparently occurs and the leukocytes accumulate for the time being in the internal organs. The degree of the shift in the leukocyte count is of value in estimating the autonomic status. Müller¹⁵ studied the reaction in detail.

We studied such reactions in the series of patients with tuberculosis. The results of the composite curves have been published elsewhere.¹⁶

CORPUSCLE/PLASMA RATIO

The corpuscle/plasma ratio has been described as of definite prognostic value in tuberculosis. Chart 15 reveals that both deaths and cases of pleural effusion are uniformly distributed.

The distribution of the clinical activity with regard to the low, medium and high values of this ratio is shown in table 30. The group

TABLE 30.—*Comparison of the Groups with the Low, the Medium and the High Values of the Corpuscles/Plasma Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Value (20 Patients)	Medium Value (40 Patients)	High Value (20 Patients)
As to Type of Tuberculosis			
Minimal.....	20%	22.5%	25%
Moderately advanced.....	10%	40%	35%
Far advanced.....	70%	37.5%	40%
	100%	100%	100%
As to Prognosis			
Good.....	40%	40%	30%
Fair.....	20%	25%	45%
Poor.....	40%	35%	25%
	100%	100%	100%
As to Weight Curve			
Gaining.....	45%	40%	40%
Stationary.....	35%	45%	45%
Losing.....	20%	15%	15%
	100%	100%	100%

15. Müller, E. F.: München. med. Wchnschr. 70:1113, 1923.

16. Petersen, W. F., and Levinson, S.: Am. Rev. Tuberc. 18:839, 1928.

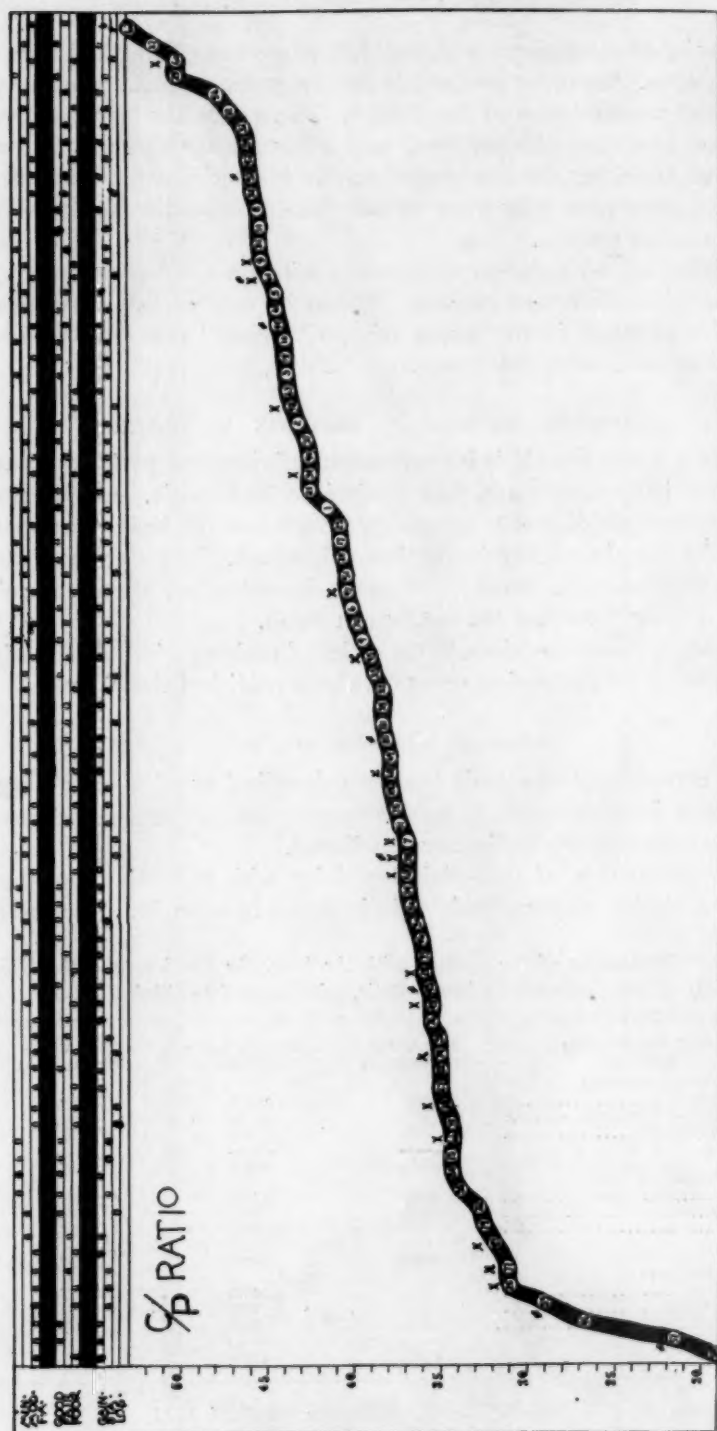


Chart 15.—The curve of the corpuscles/plasma ratio.

at the low end of the curve shows proportionately more cases of far advanced tuberculosis with poor prognosis. There is no relation to the weight curve.

TABLE 31.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the Corpuscles/Plasma Ratio*

Corpuscles/Plasma Ratio	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	CO ₂ Combining Power	Weight/Length Ratio	Deaths
31.70	6.94	65.4	9	10.47	10.95	1.9	9.25	56.92	1.79	6
47.42	7.66	68.1	9.48	10.55	18.51	1.75	8.77	53.14	2.05	5

When we examine table 31, in which the group at the extreme ends of the curve are compared, we observe that the K/Ca ratio is higher in the low group, as are the serum protein and the CO₂ combining power, and that, as a group, these patients with the low value of the ratio in question weigh considerably less.

ICE REACTION TIME

For our group of 100 "normal" men, the ice reaction time averaged 19 seconds, while for our group of twenty actually normal persons it was reduced to 14.5 seconds. This group with the low reaction time had an average age of 40 years. The group with tuberculosis, with an average age of 31 years, should show an ice reaction time below 14.5 seconds, and we actually found it to be 12 seconds.

The curve (chart 16) indicates that both deaths and cases with pleural effusion are more common in the patients with a short ice reaction time. On the other hand, the cases in which there was roentgenologic evidence of active tuberculosis, in our "normal" series, appear more frequently with longer ice reaction time (age?).

The clinical status of the groups represented on the ice reaction curve is shown in table 32. It seems that in the low and middle regions of the curve there are more cases of far advanced tuberculosis, while the prognosis and the weight curve appear to be somewhat better in the region of the delayed ice reaction.

Table 33, in which the groups at the extreme ends of the curve are compared in detail, also indicates that the persons with a delayed reaction have a more favorable outlook. The group with the short reaction time

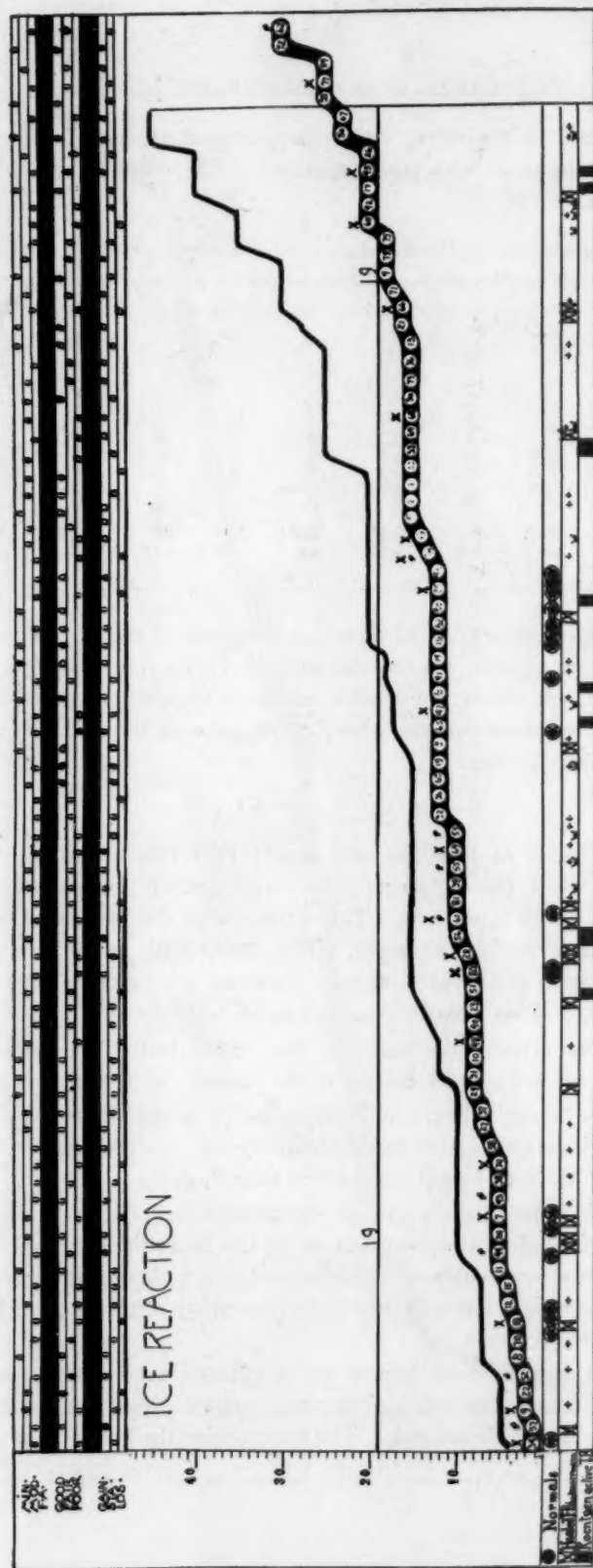


Chart 16.—The curve of the ice reaction time.

has many more cases with complications. The Kromayer light erythema time is shorter, the CO_2 combining power is higher, the wheal at the site of the injection of epinephrine is somewhat larger and the reaction to tuberculin less intense.

TABLE 32.—Comparison of the Groups with the Short, the Medium and the Long Ice Reaction Time, with Regard to Clinical Status

Clinical Classification of Patients	Short Time (20 Patients)	Medium Time (42 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal.....	10%	21%	35%
Moderately advanced.....	35%	30%	20%
Far advanced.....	55%	49%	45%
	100%	100%	100%
As to Prognosis			
Good.....	40%	35%	35%
Fair.....	35%	31%	40%
Poor.....	40%	34%	25%
	100%	100%	100%
As to Weight Curve			
Gaining.....	40%	43%	45%
Stationary.....	40%	38%	45%
Losing.....	20%	19%	10%
	100%	100%	100%

TABLE 33.—Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Time for the Reaction to Ice

Ice Reaction Time, Seconds	Bilster Time, Hours	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Ery- thema Time, Min.	CO_2 Combining Power	Age	Reaction to Epineph- rine, Wheal, Mm.	Endothelial Reaction	Reaction to Tubercu- lin, Mm.	Deaths
4	7.7	10.2	19.9	1.96	70	59.2	35.12	15.77	6+	7.1	8
20.7	7.2	10.6	19.5	1.84	98.6	55.42	31.8	14.42	9+	9.3	5
									14— 11—		

KROMAYER LIGHT REACTION TIME

The reactive erythema following upon the application of the Kromayer light appears somewhat more rapidly in tuberculous persons, as is evident in chart 17. While the time averages 120 minutes for our "normal" group, it is only 90 minutes for the patients with tuberculosis.

The clinical distribution is shown in table 34. The table shows clearly that it is impossible to correlate the reaction with any particular clinical phase.

Table 35, in which the groups at the extreme ends of the curve are compared in detail, also illustrates the relative similarity of the two groups and it is for this reason that we have included the averages. The

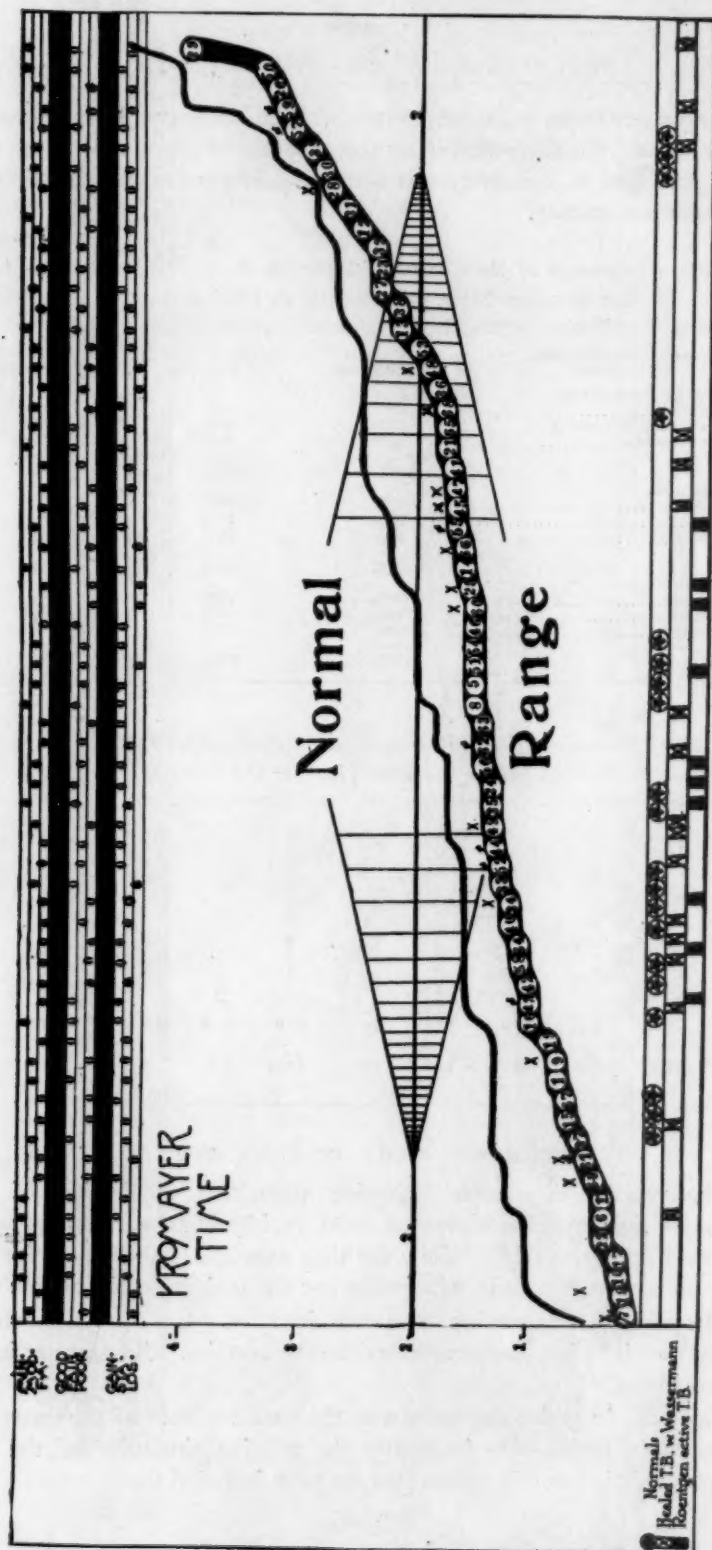


Chart 17.—The curve of the Kromayer light erythema time.

only striking difference lies in the endothelial reaction—the group with the short reaction time gives 50 per cent positive reactions as compared with 10 per cent for the group with the delayed reaction. This is confirmed when we examine the Kromayer reaction time of all the patients with the positive Rumpel-Leede endothelial reaction. It is then found to be 65 minutes as contrasted with 105 minutes for the cases in which the Rumpel-Leede endothelial reaction is negative.

TABLE 34.—*Comparison of the Groups with the Short, the Medium and the Long Time for the Appearance of Kromayer Light Erythema, with Regard to Clinical Status*

Clinical Classification of Patients	Short Time (20 Patients)	Medium Time (25 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal.....	25%	16%	20%
Moderately advanced.....	25%	32%	45%
Far advanced.....	50%	52%	35%
	100%	100%	100%
As to Prognosis			
Good.....	50%	28%	35%
Fair.....	0	44%	30%
Poor.....	50%	28%	35%
	100%	100%	100%
As to Weight Curve			
Gaining.....	35%	56%	25%
Stationary.....	45%	28%	65%
Losing.....	30%	16%	10%
	100%	100%	100%

TABLE 35.—*Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Time for the Appearance of the Kromayer Light Erythema*

Kromayer Light Erythema Time, Min.	Bilateral Time, Hours	Capillary Permeability	Inflammatory Index	Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Reaction to Morphine, Wheal, Mm.	Reaction to Morphine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Endothelial Reaction	Deaths
35.8	7.62	65.8	8.8	16.57	7.2	7.4	5.1	7.35	3.72	10+	0
153.1	7.6	67.8	9.3	15.26	6.25	6.92	4.15	8.82	3.12	10— 2+ 18—	0

MC CLURE-ALDRICH TEST

The disappearance time of intracutaneously injected salt solution, as suggested by McClure-Aldrich, seems of considerable interest in tuberculosis. Chart 18 shows that in our tuberculous patients this time varied from 15 to 190 minutes. Deaths occur more frequently in the low part of the curve; pleural effusion is more common at the high end.

The clinical status of the cases as classified on the curve is recorded in table 36. In general, the distribution of minimal, moderately advanced and far advanced tuberculosis is practically equal; the prognosis is somewhat better in the cases with delayed absorption and the weight curve is decidedly more favorable at the upper end of the curve.

TABLE 36.—Comparison of the Groups with the Short, the Medium and the Long Resorption Time for Salt Solution, with Regard to Clinical Status

Clinical Classification of Patients	McClure-Aldrich Salt Solution Disappearance Test		
	Short Time (20 Patients)	Medium Time (39 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal.....	25%	25%	15%
Moderately advanced.....	25%	28%	35%
Far advanced.....	50%	47%	50%
	100%	100%	100%
As to Prognosis			
Good.....	30%	39%	40%
Fair.....	30%	30%	40%
Poor.....	50%	34%	20%
	100%	100%	100%
As to Weight Curve			
Gaining.....	30%	38%	65%
Stationary.....	35%	48%	20%
Losing.....	35%	14%	15%
	100%	100%	100%

TABLE 37.—Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Disappearance Time for Salt Solution (McClure-Aldrich Test)

NaCl Disappearance Time (McClure-Aldrich Test)	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Min.	Ice Reaction, Seconds	Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Reaction to Tuberculin, Mm.	Deaths
42.4	70.4	9.99	10.48	19.5	1.86	79.7	8.75	15.7	5.08	8.3	2.67	5.5	3
117.3	65.46	8.86	9.8	19.25	1.96	102.7	11.3	13.66	7.53	9.6	2.96	10.4	3

When we compare the groups at the extreme ends of the curve (table 37), the following points seem of interest: There are no apparent differences in the amount of globulin; in the group with the short time, the protein is 8.5 per cent as compared with 9 per cent for the group with the delayed disappearance. The group with the short time has greater permeability of the capillaries, a higher inflammatory index, more calcium, and much shorter Kromayer and ice reaction times. The wheal at the site of the injection of epinephrine is larger, but the flare is smaller, as is also the thyroxin wheal and the reaction to tuberculin.

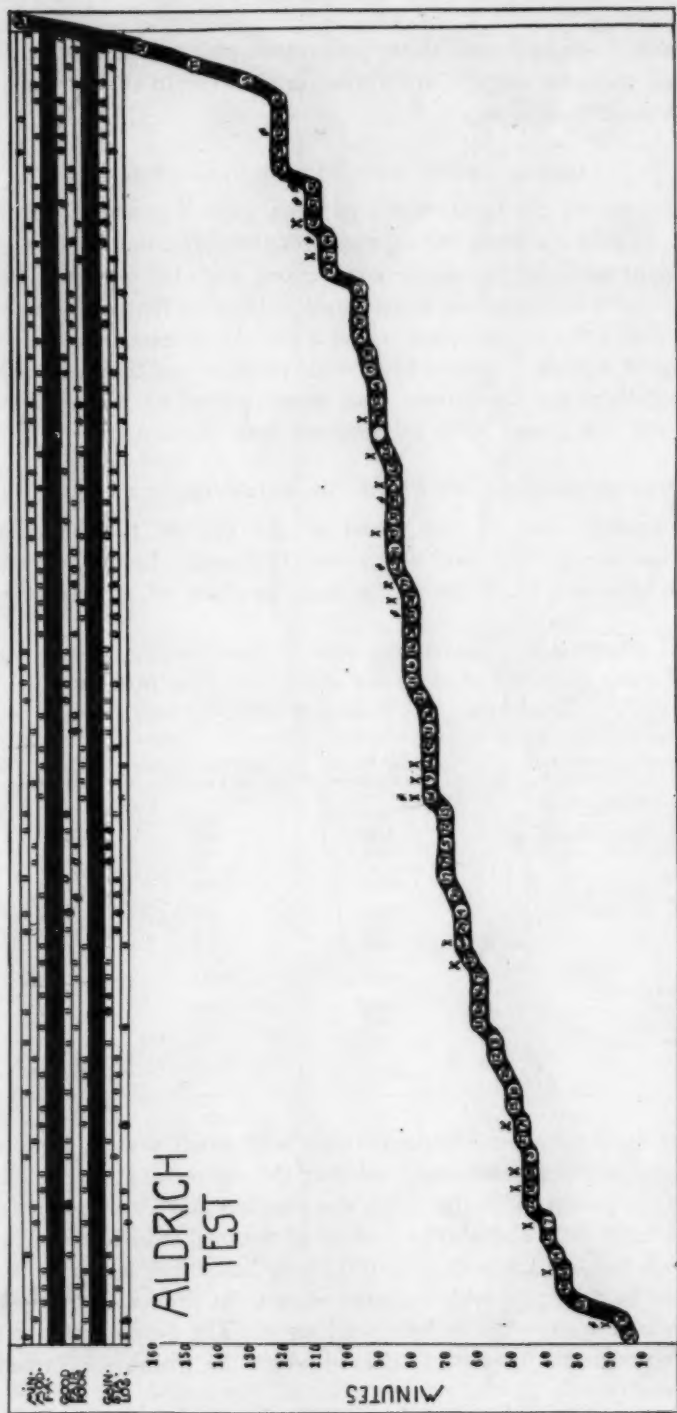


Chart 18.—The curve of the disappearance time of the salt solution in the McClure-Aldrich test.

Feldman¹⁷ studied some thirty patients ill with terminal tuberculosis and found that the shortest absorption times were in the patients with the most toxic condition.

RUMPEL-LEEDE ENDOTHELIAL REACTION

Thirty-two of the eighty-three patients gave a positive endothelial reaction. These patients were proportionately distributed among the groups with minimal, moderately advanced and far advanced tuberculosis. There may be some significance in the fact that only one of the patients with the positive reaction had a pleural effusion; that one third of them gave a primary sympathetoconic reaction and that their average Kromayer light erythema time was shortened to 65 minutes. (The average for the group with tuberculosis was 90 minutes.)

INTRACUTANEOUS REACTION TO EPINEPHRINE: WHEEL

The average size of the wheal at the site of the injection of epinephrine in our "normal" series was 19.2 mm. In the tuberculous group, it averaged 15.2. From the curve in chart 19, it may be noted

TABLE 38.—*Comparison of the Groups with the Smallest, the Medium and the Largest Diameters of the Wheal at the Site of the Injection of Epinephrine, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (30 Patients)	Medium Wheal (42 Patients)	Large Wheal (30 Patients)
As to Type of Tuberculosis			
Minimal.....	0	23%	20%
Moderately advanced.....	55%	23%	25%
Far advanced.....	45%	44%	55%
	100%	100%	100%
As to Prognosis			
Good.....	10%	46%	40%
Fair.....	50%	21%	30%
Poor.....	40%	33%	30%
	100%	100%	100%
As to Weight Curve			
Gaining.....	35%	46%	33%
Stationary.....	40%	31%	60%
Losing.....	25%	23%	7%
	100%	100%	100%

that more deaths occurred in the patients with small wheals, while cases with pleural effusion were scattered over the entire range. The clinical status of the groups with the small, the medium and the large wheals is shown in table 38. There are no cases of minimal manifestation in the group with the small wheals, and the group has either a fair or a poor prognosis. In the group with the large wheals, the prognosis seems better and more of the cases are at least stationary. The group with the most favorable prognosis seems to be that in which the wheal is intermediate.

17. Feldman, A.: Intradermal Salt Solution Test in Tuberculosis, Arch. Int. Med. 41:549 (April) 1928.

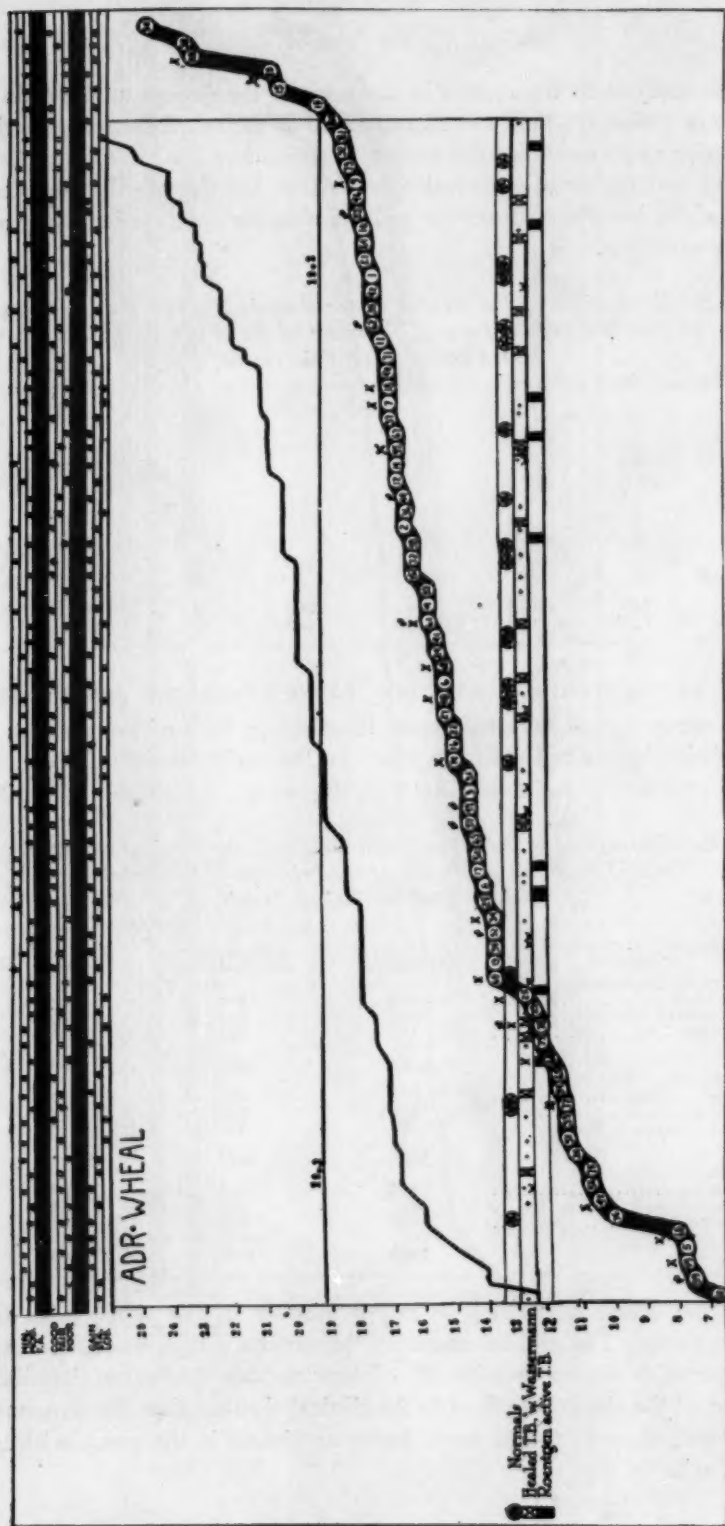


Chart 19.—The curve of the intracutaneous reaction to epinephrine (wheal).

The analysis of the results in the tests of the groups at the ends of the curve (table 39) indicates that the flare of the reaction to epinephrine and capillary permeability are somewhat greater in the group with large wheals; and the same observation holds true for the reaction to tuberculin. The absorption time for sodium chloride solution in this group is somewhat less.

TABLE 39.—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Wheal at the Site of the Injection of Epinephrine*

Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Capillary Permeability	Kromayer Light Erythema Time, Min.	Age	NaCl Resorption Time, Minutes	Reaction to Tuberculin, Mm.	Deaths
10.47	8.32	68.6	110	29.6	82.5	9.2	8
19.22	7.844	67.6	85.8	34.5	69.1	11.9	4

INTRACUTANEOUS REACTION TO EPINEPHRINE: FLARE

In our group of "normal" men, the average flare of the reaction to epinephrine had a radius of 8.8 mm. In the patients with tuberculosis, it had a radius of 6.8 mm. As with the wheal, the curve (chart 20)

TABLE 40.—*Comparison of the Groups with the Small, the Medium and the Large Radii of the Flare at the Site of the Injection of Epinephrine, with Regard to Clinical Status*

Clinical Classification of Patients	Small Flare (20 Patients)	Medium Flare (42 Patients)	Large Flare (20 Patients)
As to Type of Tuberculosis			
Minimal.....	25%	23%	15%
Moderately advanced.....	30%	31%	40%
Far advanced.....	45%	46%	45%
	100%	100%	100%
As to Prognosis			
Good.....	30%	35%	40%
Fair.....	30%	20%	40%
Poor.....	35%	30%	20%
	100%	100%	100%
As to Weight Curve			
Gaining.....	40%	38%	55%
Stationary.....	50%	42%	30%
Losing.....	10%	20%	15%
	100%	100%	100%

shows the deaths occurring in larger number in the group with the smaller flares. The clinical status of the groups with the small and the large flares is shown in table 40. There appears to be no significant relation of the size of the flare to the clinical classification, the prognosis or the weight curve; many more deaths are found in the group with the small flares.

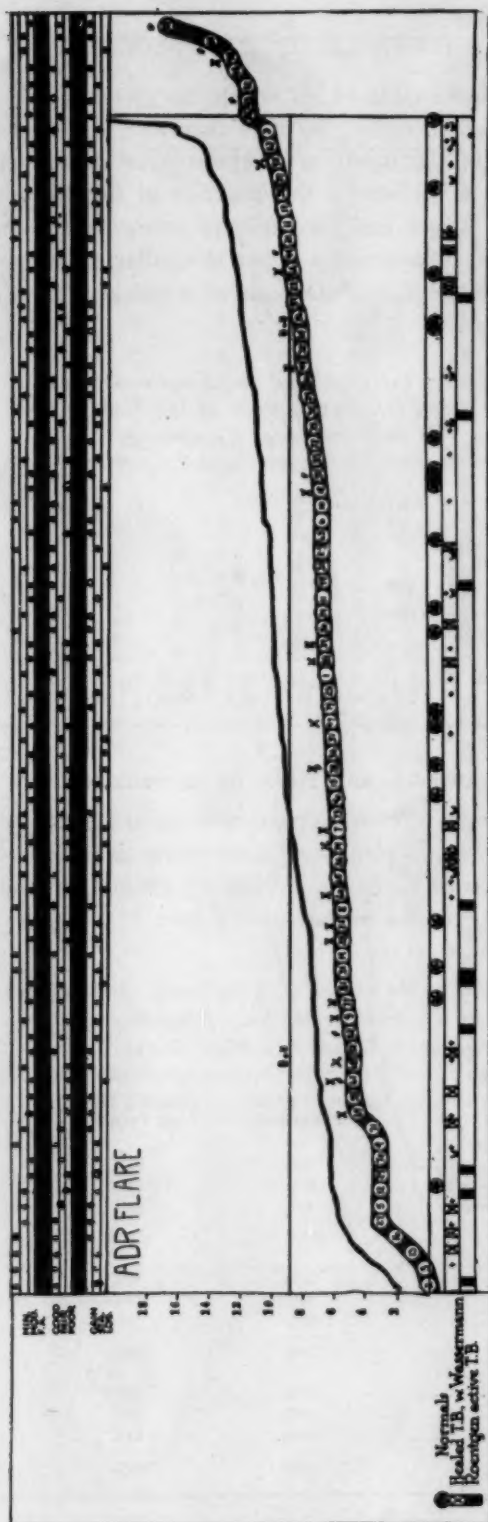


Chart 20.—The curve of the intracutaneous reaction to epinephrine (flare).

When we examine table 41, in which the group at the ends of the curve are compared in detail, we note that with the smaller flare the wheal at the site of the injection of epinephrine is somewhat smaller, and also the flare at the site of the injection of thyroxin. The blister time is somewhat longer and the capillary permeability relatively diminished so that the inflammatory index is smaller. The absorption of the sodium chloride solution is also somewhat quicker. The value of the K/Ca ratio is lower.

TABLE 41.—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Radii of the Flare at the Site of the Injection of Epinephrine*

Reaction to Epinephrine, Flare, Mm.	Reaction to Epinephrine, Wheal, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mm.	K/Ca Ratio	Kromayer Light Erythema Time, Mm.	CO ₂ Combining Power	NaCl Resorption Time, Minutes	Deaths
3.691 10.56	13.82 15.8	9.35 8.75	3.25 6.5	8 7.1	62.5 69.3	8.8 10	10.7 10.4	18.55 20.2	1.75 1.66	96.8 77.8	54.9 58.1	73.6 81.2	9 2

INTRACUTANEOUS REACTION TO THYROXIN: WHEAL

There seems to be no characteristic relation of the mortality nor any relation of the cases with pleural effusion to the size of the wheal at the site of the injection of thyroxin. When we examine the clinical status of the patients as grouped in the curve (chart 21), it would seem that

TABLE 42.—*Comparison of the Groups with the Small, the Medium and the Large Diameters of the Wheal at the Site of Injection of Thyroxin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (20 Patients)	Medium Wheal (42 Patients)	Large Wheal (20 Patients)
As to Type of Tuberculosis			
Minimal.....	30%	28%	0
Moderately advanced.....	25%	30%	35%
Far advanced.....	45%	42%	65%
	100%	100%	100%
As to Prognosis			
Good.....	50%	45%	5%
Fair.....	25%	29%	45%
Poor.....	25%	26%	50%
	100%	100%	100%
As to Weight Curve			
Gaining.....	25%	45%	55%
Stationary.....	55%	42%	20%
Losing.....	20%	13%	25%
	100%	100%	100%

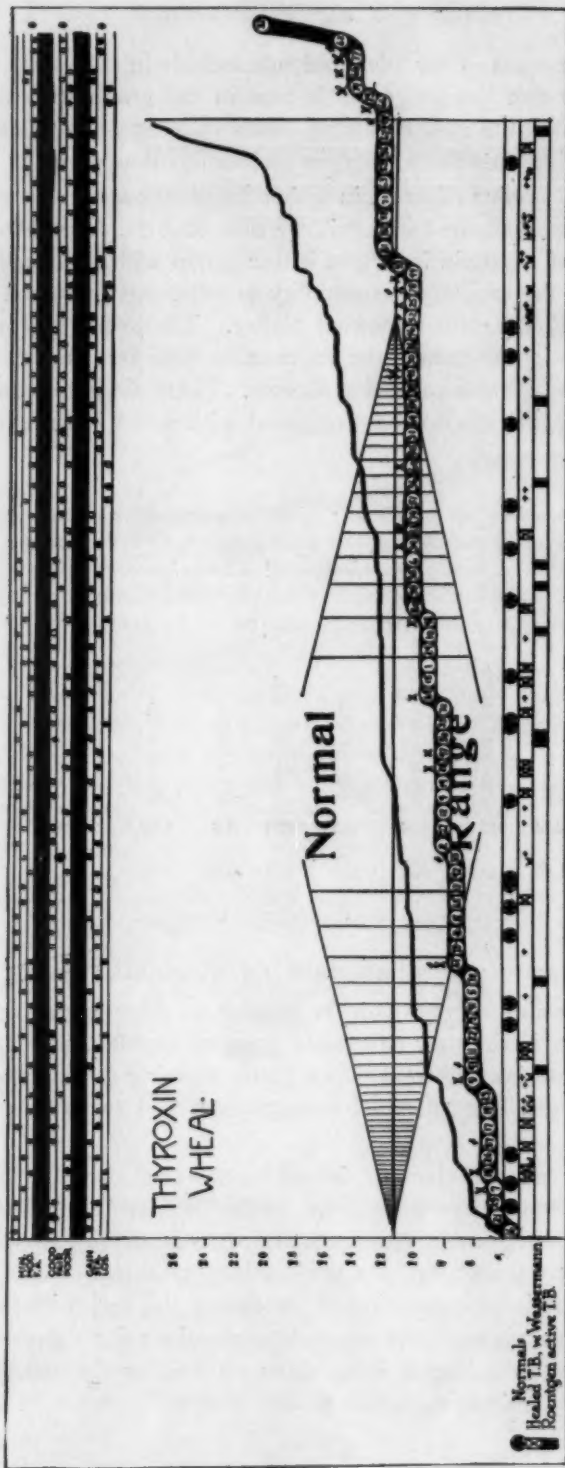


Chart 21.—The curve of the intracutaneous reaction to thyroxin (wheal).

there are more cases of far advanced tuberculosis in the group with the larger wheals, that the prognosis is best in the group with the small wheals, and that the gain in weight seems to be most favorable in the groups at the intermediate and upper portions of the curve.

When we examine table 43, in which the groups at the extreme ends of the curve are compared in detail, we note that the flare at the site of the injection of thyroxin is largest in the group with the small wheals, in whom also the capillary permeability is somewhat increased and the value of the K/Ca ratio somewhat higher. The average protein percentage is less in the group; the ice reaction time and the salt solution absorption time are also somewhat shorter. There are nine persons with positive endothelial reactions as compared with seven in the group with larger wheals.

TABLE 43.—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Wheal at the Site of Injection of Thyroxin*

Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium Mg.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	Ice Reaction Time, Seconds	Endothelial Reaction	NaCl Absorption Time, Minutes	Deaths
5.35	3.05	7.72	67.3	9.47	10.2	19.3	1.9	8.341	9.6	11+	75.2	6
12.5	0.92	6.95	63.9	9.38	10.3	18.1	1.75	9.338	13.8	9— 7+ 13—	85.2	7

INTRACUTANEOUS REACTION TO THYROXIN: FLARE

As twenty-nine of our patients showed no flare at the site of the injection of thyroxin, they have been grouped together, and the rest of the material has been divided into a group showing a small flare and a group showing a large flare of twenty-seven and twenty-six patients, respectively.

From the curve in chart 22, it will be observed that the flare in the tuberculous group is less marked than in the "normal" and miscellaneous clinical groups previously examined, and that the deaths, as well as the cases with pleural effusion, are uniformly distributed. Table 44 indicates that there is no correlation of the size of the flare with the clinical status. The averages of the other determinations for the groups with the smallest and the largest flares show no striking differences and we have therefore omitted the tables.

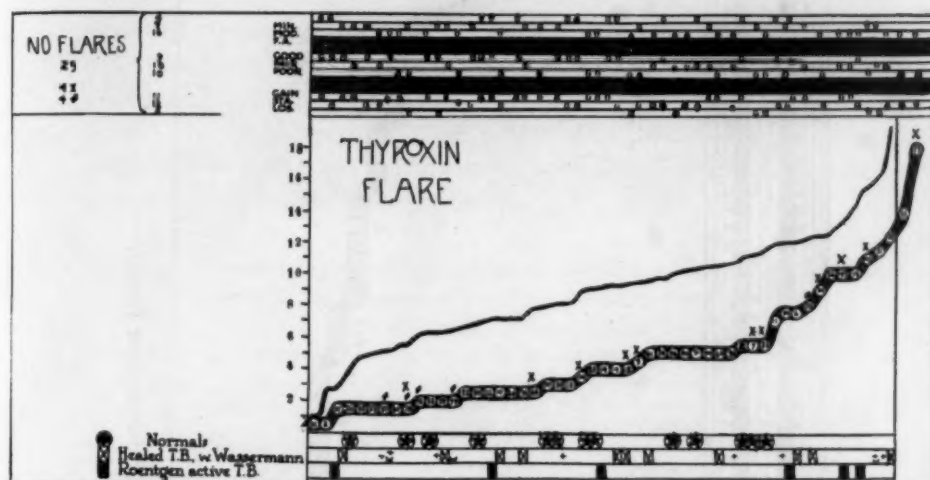


Chart 22.—The curve of the intracutaneous reaction to thyroxin (flare).

TABLE 44.—Comparison of the Groups with the Small, the Medium and the Large Radii of the Flare at the Site of Injection of Thyroxin, with Regard to Clinical Status

Clinical Classification of Patients	Small Flare (29 Patients)	Medium Flare (27 Patients)	Large Flare (23 Patients)
As to Type of Tuberculosis			
Minimal.....	13%	33%	20%
Moderately advanced.....	31%	37%	27%
Far advanced.....	56%	30%	53%
	100%	100%	100%
As to Prognosis			
Good.....	30%	60%	20%
Fair.....	34%	14%	42%
Poor.....	36%	26%	38%
	100%	100%	100%
As to Weight Curve			
Gaining.....	37%	60%	27%
Stationary.....	45%	30%	50%
Losing.....	18%	10%	23%
	100%	100%	100%

REACTION TO TUBERCULIN¹⁸ (TWENTY-FOUR HOURS)

The size of the reaction at the site of the injection of tuberculin, as measured after twenty-four hours, varied in our series from 0 to 28.5 mm. The curve in chart 23 illustrates the series. If we divide the group into those with negative or small, those with intermediate and

18. Long's Synthetic Tuberculin used.

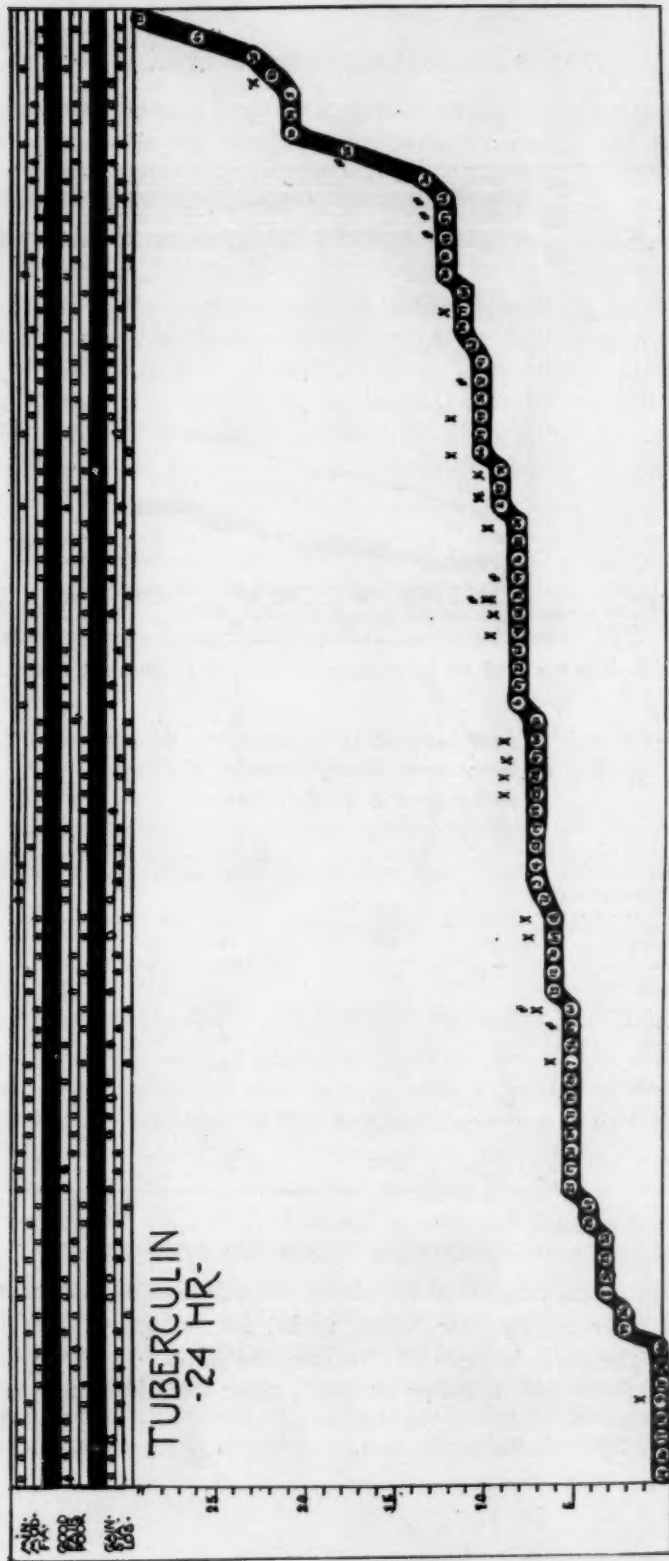


Chart 23.—The curve of the reaction to tuberculin (at twenty-four hours).

those with large reactions, we find that there are more cases of minimal manifestation in the group with small reactions and more cases of far advanced tuberculosis in the group with large reactions. There appears to be absolutely no difference in the clinical prognosis as between these groups and no clearcut difference as far as the weight curve is concerned. It will also be observed that the deaths are distributed largely in the center of the curve and that the cases with pleural effusion seem to be associated with somewhat larger flares.

TABLE 45.—*Comparison of the Groups with the Small, the Medium and the Large Diameters of the Reaction at the Site of Injection of Tuberculin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (24 Hours) (20 Patients)	Medium Wheal (24 Hours) (41 Patients)	Large Wheal (24 Hours) (20 Patients)
As to Type of Tuberculosis			
Minimal.....	45%	14%	15%
Moderately advanced.....	25%	30%	30%
Far advanced.....	40%	50%	55%
	100%	100%	100%
As to Prognosis			
Good.....	45%	29%	35%
Fair.....	35%	24%	45%
Poor.....	20%	47%	20%
	100%	100%	100%
As to Weight Curve			
Gaining.....	35%	41%	55%
Stationary.....	55%	31%	35%
Losing.....	10%	28%	10%
	100%	100%	100%

In table 46, in which the groups at the extreme ends of the curve are compared, it may be noted that in the low group there is more potassium and less cholesterol and a smaller wheal at the site of the injection of thyroxin, but a flare somewhat larger. The salt solution absorption time is less, but the value of the corpuscles/plasma ratio is somewhat increased.

REACTION TO TUBERCULIN (PERSISTENT)

When we now take into consideration the persistency of the reaction (chart 24), we again find that there is no direct relation to the deaths. The relation to clinical status is shown in table 47. Again, the patients with the persistent and most marked flares (upper end of the curve) show a preponderance of cases of far advanced tuberculosis; there is apparently little difference between the groups as to prognosis, and the weight curve is most favorable at the end representing the most persistent and largest reactions.

TABLE 46.—Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Reaction at the Site of Injection of Tuberculin

Reaction to Tuberculin, Mm.	Blister Time, Hours	Capillary Permeability	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	Cholesterol, Mg.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	NaCl Absorption Time, Minutes	Corpuscles/Plasma Ratio	CO ₂ Combining Power	Deaths
2.2	7.7	67	10.3	20.2	1.96	8.3	185	2.1	4.1	65	41.3	56.3	2
14.7	7	67	10.2	18.7	1.84	8.902	207	9.3	2.9	90	38.7	55.6	2

TABLE 47.—Comparison of the Groups with the Persistent Small, Persistent Medium and Persistent Large Reaction at the Site of Injection of Tuberculin, with Regard to Clinical Status

Clinical Classification of Patients	Small Reaction (20 Patients)	Medium Reaction (42 Patients)	Large Reaction (20 Patients)
As to Type of Tuberculosis			
Minimal.....	30%	14%	30%
Moderately advanced.....	40%	43%	5%
Far advanced.....	30%	43%	65%
	100%	100%	100%
As to Prognosis			
Good.....	40%	31%	45%
Fair.....	25%	35%	25%
Poor.....	35%	34%	30%
	100%	100%	100%
As to Weight Curve			
Gaining.....	20%	50%	45%
Stationary.....	65%	31%	40%
Losing.....	15%	19%	10%
	100%	100%	100%

TABLE 48.—Comparison of the Groups with the Negative, the Medium and the Marked Tuberculosis Complement Fixation, with Regard to Clinical Status

Clinical Classification of Patients	Negative Fixation (20 Patients)	Medium Fixation (37 Patients)	High Fixation (20 Patients)
As to Type of Tuberculosis			
Minimal.....	50%	16%	0
Moderately advanced.....	30%	30%	40%
Far advanced.....	20%	54%	60%
	100%	100%	100%
As to Prognosis			
Good.....	55%	40%	5%
Fair.....	15%	32%	45%
Poor.....	30%	28%	50%
	100%	100%	100%
As to Weight Curve			
Gaining.....	30%	48%	40%
Stationary.....	55%	35%	30%
Losing.....	15%	17%	30%
	100%	100%	100%

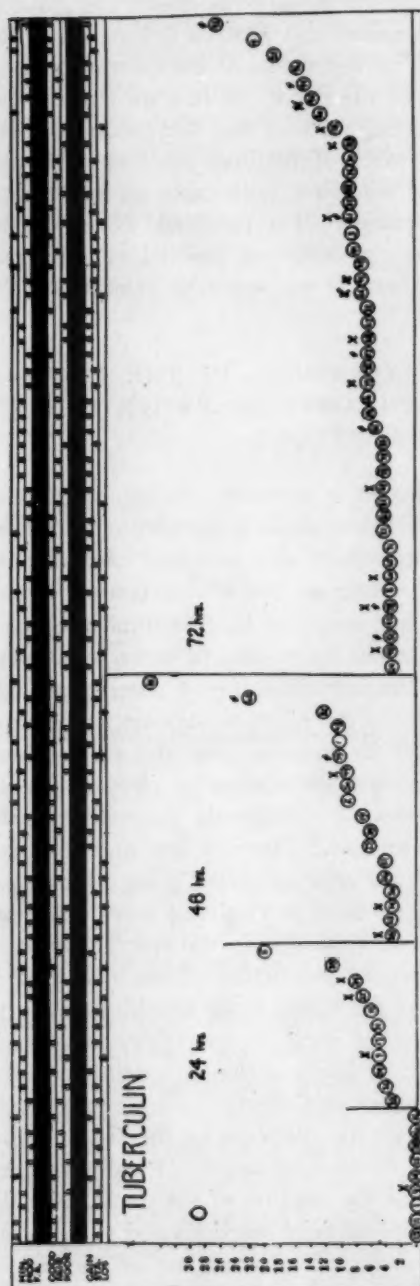


Chart 24.—The curve of the reaction to tuberculin (persistent).

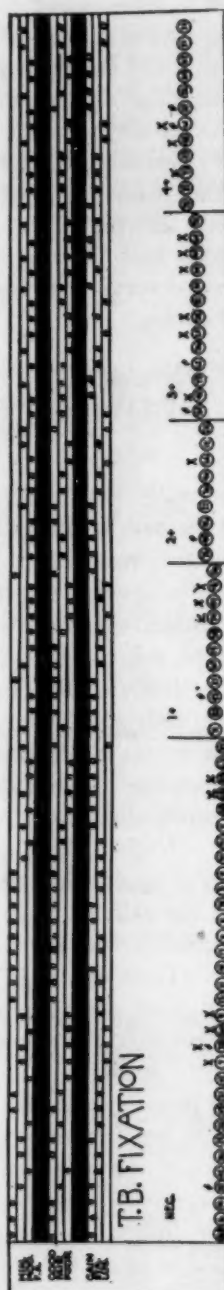


Chart 25.—The curve of tuberculosis complement fixation.

TUBERCULOSIS COMPLEMENT FIXATION

As the complement fixation reaction so largely follows the globulin and Daranyi reactions, we have prepared only a curve (chart 25) of the material, and have not made tables of the results of the examinations of the patients at the extreme ends of the curve. When we classify our material on the basis of this reaction, we find that the group with the negative reactions contains more cases of minimal manifestation, and the group with the most marked reactions, only cases of moderately advanced and far advanced tuberculosis. The prognosis is best in the low group and becomes increasingly poor as we proceed to the group with more marked reactions. There is no apparent relation to the weight curve.

C. CLINICAL STUDY OF ALTERATIONS IN THE PERMEABILITY OF THE CAPILLARIES IN PATIENTS WITH TUBERCULOSIS

The material presented here makes it apparent, we believe, that so far as the patient with pulmonary tuberculosis is concerned, increased inflammatory reactivity is usually associated with increased clinical activity. With lessened constitutional reactivity, the clinical course is relatively benign. It is self-evident that one must keep in mind the many exceptions, the fact that the tuberculous lesion may be cured by absorption, that many of our forms of therapy make use of stimulation, etc.

Practically, our therapy consists in the effort to support normal and inherent forces of resistance either by insuring rest and proper food or by recourse to methods of moderate stimulation by physical agents.

Theoretically, three major lines of therapeutic approach to the problem of tuberculosis can be discerned. There is first and foremost the field of specific immunity, with the attack directed toward the virus; of late, the cellular aspect of the problem is receiving more attention. The second is fundamentally chemotherapeutic in the specific sense of Ehrlich. Here, again, it is the specific destruction of the virus that is the immediate goal, the reaction of the tissue being considered only to the degree that the agent shall not of itself be too toxic. Even this apparently straight line of attack is being seriously questioned, and modern investigators (the recent paper of Seifert,¹ for instance) would now place much greater emphasis on the reactions of the tissue to the injection of the so-called specific therapeutic agent. Finally, a third line of approach takes cognizance of the reaction of the tissue, with the endeavor directed toward promoting beneficial reactions and suppressing unfavorable ones. Perhaps the enzymatic destruction of bacteria, a

1. Seifert, W.: *Klin. Wchnschr.* 7:1497, 1928.

both epinephrine and pituitary⁹ in our experiments on lymph. The former has the disadvantage that it has so marked an effect on sympathetic nerve endings, increases the metabolic rate and, particularly in the tuberculous, may result in paradoxical effects. Dextro-epinephrine might obviate some of these defects. Pituitary seems to act well when injected in slowly absorbable form. It has the additional advantage that its effect is apparent even on irritated capillaries, when epinephrine fails. As the effect of these agents on capillary permeability is of considerable interest, we have performed an experiment in a dog, in which epinephrine (1 mg.) and pituitary in oil (dosage corre-

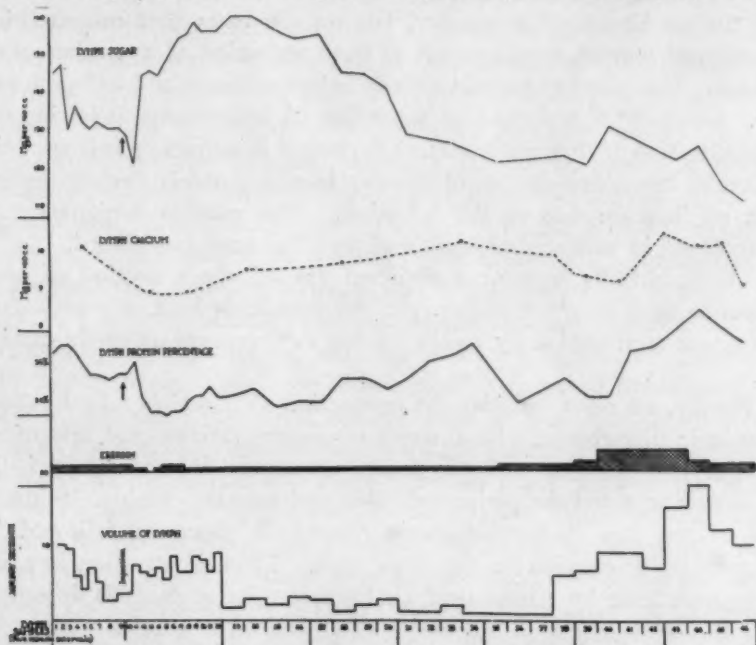


Chart 1.—Effect of injection of epinephrine and pituitrin on lymph volume, lymph concentration, lymph sugar, lymph calcium and erepsin.

sponding to one therapeutic dose in man) were given intramuscularly. The long continued diminution of the lymph flow after the primary increase due to increased blood pressure and the diminution in the concentration of protein indicate the change in permeability. The lowering of the calcium of the lymph is in line with this change.

Calcium.—The value of the administration of calcium is problematic. The fault is not necessarily in a deficiency of calcium in the fluids, but in the fact that calcium, because of the vegetative status, is not fixed by the cells. The mere increase of the calcium of the plasma

9. Petersen, W. F., and Hughes, T. P.: J. Biol. Chem. **66**:229, 1925.

produced by the administration of calcium can have little effect, nor will the use of parathyroid hormone be of avail (as recently demonstrated by Gordon, Roark and Lewis,¹⁰) because in that case one is merely taking calcium from tissue reserves to increase it in the fluids of the body. Nevertheless, it may be useful in cases in which a relatively low calcium level can be demonstrated in the plasma and the tissues are able to fix the excessive calcium offered them.

Diminution of the Activity of the Sex Glands and of the Thyroid Gland.—Diminution of the activity of the sex gland in women is of obvious therapeutic importance, not only with the idea of sterilization and the avoidance of pregnancy, but on the basis that menstruating tuberculous women are more apt to have activation of the tuberculous process. The effect of thyroid activity is less apparent and still problematic. Coulaoud¹¹ described an activation of tuberculosis following the administration of thyroid extract. On general principles, lowering of the metabolic rate might be useful in cases in which one is already dealing with an increase due to the infection. The relative benignancy of tuberculosis in castrated animals and man has been established.

Therapeutically, measures designed toward the reduction of such endocrine activity are available. In the female, at least, a transient or permanent sterilization by means of the roentgen ray is easily carried out.

Finally, we must consider the production of a peripherally localized autonomic disturbance. In a series of papers, Müller and one of us (W.F.P.)¹² demonstrated the close autonomic interrelation of the splanchnic area and the peripheral (skin and muscles) region. Stimulation of the one (parasympathetic status) is promptly followed by sympathetic orientation in the other area. Thus, if the skin is made parasympathetic by stimulation (a burn, an intracutaneous injection, etc.) the splanchnic area becomes sympathetic in its general tonus. If, for instance, one wishes to alter the vascular status of a peritoneal tuberculosis, this may be done by producing a superficial effect on the skin. As a matter of fact, this has been suggested empirically in the treatment of tuberculous peritonitis, an ultraviolet burn of an area approximately 10 by 10 cm. being used.

One has, then, a series of measures available which, either singly or in combination, might influence the general reaction of the tuberculous person by altering the rate of absorption of toxic material from the foci of the disease.

10. Gordon, B.; Roark, J. L., and Lewis, A. K.: Effect of Parathyroid Hormone on Certain Signs and Symptoms in Tuberculosis, J. A. M. A. **86**:1683 (May 29) 1926.

11. Coulaoud, E.: Médecine **3**:627, 1923.

12. Müller, E. F., and Petersen, W. F.: Klin. Wchnschr. **5**:1025, 1926.

field of endeavor that has occupied Russian investigators chiefly, should be mentioned. A recent paper of Platonov² is one of a group that deals with a possible therapy along these lines.

We do not wish to enter into a theoretical discussion of any length in this part of the work, but we should like to emphasize the third method of therapeutic approach, namely, the endeavor to change the reaction of the host toward the infection. In this problem, the question of the capillary permeability (to proteins, etc.) immediately comes to the foreground and it is only this phase that we wish to discuss at this time. Four premises are to be taken into consideration.

1. Schade³ recently determined that the reaction of tuberculous tissue is toward the acid side (p_H of 6.5) exactly at the optimum for the growth of tubercle bacilli. The capillaries normally respond to an acid reaction by dilatation and increased permeability.

2. The autonomic nervous system, as part of the general vegetative balance is obviously involved. Not only have the studies of Guth,⁴ Glaser⁵ and others made this probable, but the pioneer work of Pottenger in this country in relation to symptomatology emphasized it. Unfortunately, conflicting concepts and terminology have obscured the work in this field. Epinephrine makes the capillary endothelium less permeable. It is, however, the representative agent for producing sympathetic effects. The "sympatheticotonic" person, on the other hand, has more permeable capillaries and the blood pressure may be low. We think of the state of tissues with contracted vessels and less permeable capillaries as the typical rest stage. Yet in many persons the injection of epinephrine hydrochloride lowers the blood pressure and increases the permeability. The so-called "vagotonic" person usually has a higher blood pressure, a lower metabolic rate and less permeable capillaries. Yet stimulation of so-called parasympathetic nerves commonly results in dilatation of the vessels and increased permeability, i. e., tissue activity. Obviously, much of the confusion results from the transfer of strictly anatomic concepts and terms to the autonomic nervous apparatus, instead of starting out on a purely functional basis (see the discussion of Kraus' concept). Relatively impermeable capillaries (an effect of epinephrine and pituitary?) are usually found associated with relatively chronic tuberculosis, and greater permeability with active tuberculosis (effect of thyroid?).

3. Even specific agents (tuberculin, sodium aurothiosulphate, sodium cinnamate, etc.) act on the capillaries, usually rendering them

2. Platonov, G.: *J. Infect. Dis.* **14**:549, 1926.

3. Schade, H.: *Ztschr. f. d. ges. exper. Med.* **49**:334, 1926.

4. Guth, E.: *Beitr. z. Klin. d. Tuberk.* **60**:39, 1924.

5. Glaser, W.: *Beitr. z. Klin. d. Tuberk.* **55**:390, 1923.

more permeable for a time, and later diminishing their permeability. The focal reaction, whether in the form that is obvious clinically, or consisting merely of practically imperceptible biologic reactions following in the wake of minute doses of various agents, is a reaction that depends on changes in the permeability of the capillaries about the focus.⁶

4. Various biologic influences (endogenous or exogenous), among them menstruation, the effect of the season, etc., which are distinctly associated with increased permeability and autonomic instability are frequently found associated with distinct clinical evidences of activation.

The conclusion might seem warranted that increase in capillary permeability, however produced, unfavorably influences a tuberculous process.

METHODS OF DIMINISHING PERMEABILITY

Granted these simple premises, how can one proceed to bring about diminished permeability of the tissues? Several possibilities may be considered:

1. Alkalinization.
2. Agents acting directly on cell membranes, chiefly epinephrine and pituitary (perhaps insulin).
3. Increasing the calcium of the plasma.
4. Diminishing the activity of the thyroid or of the sex glands.
5. Producing a peripheral regional (skin and muscles) autonomic stimulus with resulting compensation in the visceral area.

Alkalinization.—In its general effects alkalinization must make tissues less permeable, for the converse, local acidosis, makes the capillaries dilate and the endothelial cells more permeable. Modrakowski and Lentz have recently confirmed this.^{6a} It must be kept in mind that with the usual methods at one's disposal, alterations produced by therapeutic measures (administration of citrates, the Sippy diet, etc.) are never pronounced and, at best, the CO₂ combining power is increased to only a minor degree. Jordan's work⁷ indicates that there may be considerable difference in the effect, however, in different persons.

Epinephrine and Pituitary.—Both epinephrine and pituitary diminish the permeability of cells, even in high dilution. Langer⁸ demonstrated this effect for epinephrine and we showed the same effect for

6. Levinson, S. A., and Petersen, W. F.: *Am. Rev. Tuberc.* **15**:6, 1927.

6a. Modrakowski, G., and Lentz, R.: Abstracts, International Physiological Congress, Boston, 1929, p. 184.

7. Jordan, S. M.: Calcium Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, *J. A. M. A.* **87**: 1906 (Dec. 4) 1926.

8. Langer: *Ztschr. f. physiol. Chem.* **118**:1, 50 and 96, 1922.

May one at the same time make the soil less favorable for the growth of the organism? This is a question that only long experience and experimentation will solve. The presumptive evidence is in favor of this view, and for the following reasons: The reaction at which the tubercle bacilli seem to grow best in the human organism is at a p_H of 6.7, i.e., slightly on the acid side of neutrality. This is the range at which Schade found the caseous material of the tubercle. If one is able to alkalinize the tissues or to create a tendency toward restoration to the alkaline side, the soil might, it seems, be made less favorable.

CLINICAL OBSERVATIONS:

THE INJURIOUS EFFECT OF INCREASE IN PERMEABILITY

The first two cases concern twin sisters, 23 years of age. Both had been under observation at the municipal dispensaries for a long time and for a short time were at the Municipal Sanitarium.

Clinical History of Sister A.—The illness began with pleurisy in 1920; in 1922, there was cough with loss of 20 pounds (9 Kg.), night sweats, etc. In addition, the patient had numbness and twitching of the right arm, with some plasticity, and later of the entire right side, but this had gradually lessened. She had several convulsive seizures in February, 1924. The family history was negative. On examination, it was noted that the right shoulder drooped, and that there was marked degeneration of the subcutaneous tissues of the right arm, which was paralyzed. The condition of the lungs indicated a far advanced "C" (Turban III, right IV, left III). The temperature was 101 F. in the afternoon; the pulse rate was 120. Tubercle bacilli were found in the sputum. The urine was normal. The Wassermann reaction was negative. The tuberculosis complement fixation was ++. The hemoglobin content was 70 per cent. The red cell count was 4,750,000, and the leukocytes numbered 11,300.

The patient entered the Research and Educational Hospital in June, 1925, with essentially the same physical conditions. The roentgenogram revealed cavitation of both upper lobes and an extensive parenchymal infiltration throughout both lungs.

The infection, as determined by further investigation, probably had occurred during childhood by transmission from a seamstress who frequently worked and lived in the family. She had had an apparently active tuberculosis, and the twin sisters frequently had been in contact with her for considerable periods.

On admission, the weight of patient A was 76 pounds (34.5 Kg.). In the graphic chart of this patient (chart 2) it may be noted that the temperature and the pulse rate during the control period of observation fluctuated within a constant range. On July 4, the patient was inadvertently exposed to rather intense sunlight for several hours, and an activation was immediately apparent, the average of the maximal temperatures increasing 0.7 F.

On July 13, 15 and 17, the patient was given 2 mg. of pilocarpine in oil (intramuscular injections). Despite the fact that peripheral dilatation should be followed by a decrease in temperature, there was a marked increase both of temperature and of pulse rate (chart 2). Two weeks after the first injection of pilocarpine, the patient began to complain of severe headache; the temperature

increased markedly, delirium developed thirty-three days after the injection, and one week later the patient died with all the clinical and laboratory evidences of tuberculous meningitis.

It may be of interest to observe in chart 2 that intramuscular injections of epinephrine in oil were given the patient after the onset of the tuberculous meningitis and a striking effect on the basal metabolic rate was noted. So, too, the injection of large doses of dextro-epinephrine (5 mg. in oil on alternate days) may have influenced the temperature for a short period before death.

Autopsy (by Dr. R. H. Jaffé).—The body was that of a fairly well-built, extremely emaciated female. The skin was pale yellow-gray with several livid patches on the back. The subcutaneous fat was reduced to a yellow-brown layer, from 3 to 5 mm. thick.

The lungs were adherent to the thoracic wall by a fibrous band, especially in the upper lobes. The lower margins of the lower lobes were distended and rounded off. The posterior part of the right upper lobe contained a large irregular cavity from 2 to 3 cm. in diameter, filled with a small amount of yellow-green fluid. The walls were smooth and gray-red. Elevations corresponding to the larger vessels were present. The cavity communicated with the larger bronchi of the upper lobe. There were groups of acinose yellow-gray nodules in the center of the right lower lobe. The left lung showed an irregular cavity in the posterior part of the upper side of the lower lobe. It was 0.5 cm. in diameter and its walls were similar to those of the cavity described. About this cavity in the left lung were several small yellow nodules in areas of gray-red consolidation. Near the base of the left lower lobe was a small, round cavity with smooth, gray-white fibrinous walls, about 9 mm. in diameter. Attached to this cavity was a small, fibrous, calcified nodule with branches of scar tissue about it. The lymph glands of the hilum about the tracheal bifurcation were slightly enlarged, gray-red and soft.

The heart weighed 175 Gm. The pericardial cavity contained 100 cc. of clear, yellow fluid. The left ventricular wall was 12 mm. in diameter. The right ventricular wall was 4 mm. in diameter. The myocardium was red-brown and soft. The endocardium of the left ventricle showed a whitish thickening over the septum. There were no changes in the valves. The aortic circumference above the valves was 58 mm. Small yellow elevations about the coronary openings were found. Large, yellow-white plaques were found in the ramus ascendens of the left coronary artery.

The spleen weighed 88 Gm. It was soft and dark red, and the cut surface showed distinct structure.

The liver weighed 905 Gm. The surface was smooth and gray-brown, with irregular yellow patches on the convexity of the right lobe. These patches extended about 1 cm. into the liver tissue. The cut surface showed almost no structure.

The suprarenal glands showed the cortex gray-white, with yellow nodules, and the medulla deep brown.

The kidneys weighed, left, 135 Gm., right, 110 Gm. The capsules stripped easily. The surface of the left kidney showed distinct fetal lobulation. The cortex was gray-red, the medulla dark red.

The stomach contained a small amount of gray fluid. The mucosa had been destroyed by postmortem changes.

The cecum contained several round, superficial ulcerations from 3 to 5 mm. in diameter. The edges were notched. The mucosa was dark red; no changes appeared in the other parts of the intestine.

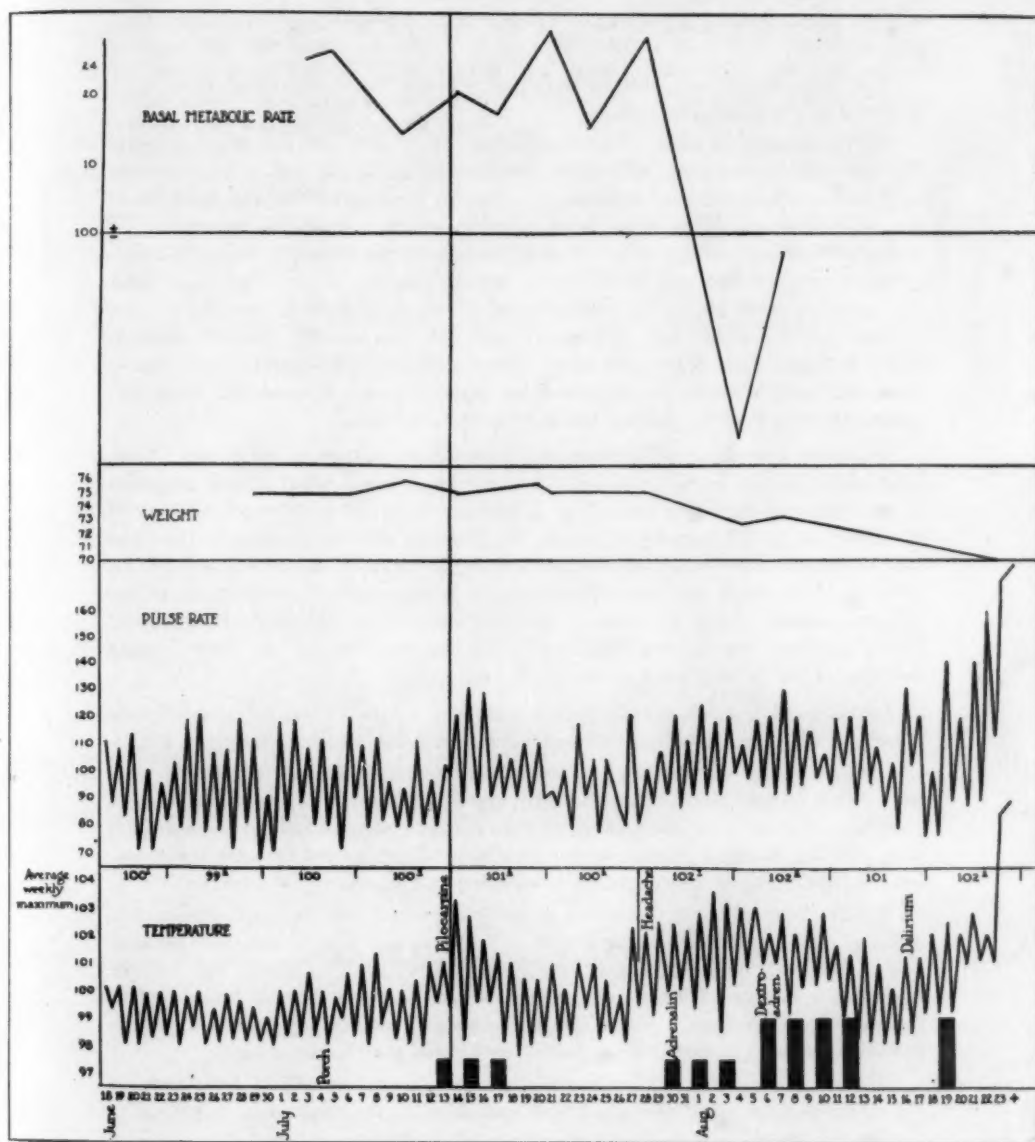


Chart 2.—Clinical record of sister A, who died from tuberculous meningitis. The patient was treated with pilocarpine and epinephrine.

The ovaries were small with deep depressions on the surface. They contained no corpora lutea. There was a small cyst in the right ovary.

The uterus was small. The mucosa was anemic.

The pancreas weighed 72 Gm. It was about 17 cm. long. The color was gray-red.

The dura mater was smooth and gray-white. Dark red blood clots were observed in the longitudinal sinus.

The brain was swollen. The convolutions were flat; the leptomeninges over the convexities were deep red. Over the base of the brain was a large amount of yellow-green, gelatinous exudate, covering the pons and filling the space about the infundibulum. Many small, gray nodules occurred along the arteria cerebri media and diffuse nodules occurred near the pole of the temporal lobe. The ventricles were distended and filled with a cloudy, gray-red fluid. The brain tissue was soft. A small thickening was observed in the meninges near the median edge of the left convexity over the upper part of the anterior central convolution. Incisions here revealed a small yellow nodule from about 3 to 5 mm. in diameter, lying between the gray and the white matter. The nodule stood out, separated from the surrounding tissue by a fine gray line.

Anatomic Diagnosis.—The diagnosis included the following conditions: large tuberculous cavities in the right upper and left lower lobes, fresh acinose eruptions in the center of the right lower lobe, submiliary tubercles in the surroundings of the cavity in the left lower lobe and an encapsulated tubercular lesion in the basal part of the left lower lobe; tuberculous meningitis; acute edema and hydrocephalus internus of the brain and old solitary tubercle in the anterior central gyrus of the left convolution; fresh tuberculous ulcers of the cecum; atrophy of the heart; cloudy swelling, edema and incipient cloudy degeneration of the liver; cloudy swelling of the kidneys and atrophy of the spleen.

Histologic Observations (Dr. Jaffé).—Spleen: Many miliary tubercles were present in the pulp. They consisted of epithelioid cells and single large giant cells.

Lungs: In the surroundings of the tuberculous cavities many acinar tubercles were found in the thickened interalveolar septums. These tubercles showed much caseation. Collagenous fibers extended between the epithelial cells of the marginal zone into the caseated centers, where they were distinguished between the tuberculous débris. Much fibrous tissue surrounded and separated the tubercles.

Brain: The nodule in the cortex of the left convexity of the brain consisted of a cheesy center, surrounded by a wall of large, round, foamy cells and lymphocytes. Between these, distended capillaries were visible. Outside the cellular zone was a capsule of dense collagenous connective tissue, stained bright red in the van Gieson sections. About this capsule was a marked proliferation of glia tissue. Distended blood-filled capillaries perforated the fibrous capsule.

Kidney: The kidneys showed little change: a diffuse capillary hyperemia of the medulla and a slight swelling of the epithelium of the convoluted tubules.

Liver: There were few submiliary tubercles. They consisted of one or two giant cells, a group of lymphocytes and a thick capsule of hyaline connective tissue, which extended into the center of the nodules.

The heart revealed marked pigmentation of the myocardial fibers. The suprarenal glands showed the lipid content of the cortex much diminished, and hyperemia of the reticulum. No changes were noted in the pancreas.

THE CONVERSE

We turn now to the converse of this picture.

Clinical History of Sister B.—The twin sister B entered the Municipal Sanitarium with patient A (July, 1924). She gave a history of pleuritic pains, abdominal pain, loss of 20 pounds (9 Kg.), and cough, which had been present for a year. In February, 1924, she had an acute exacerbation, with chills and sweats, and was in bed for ten weeks.

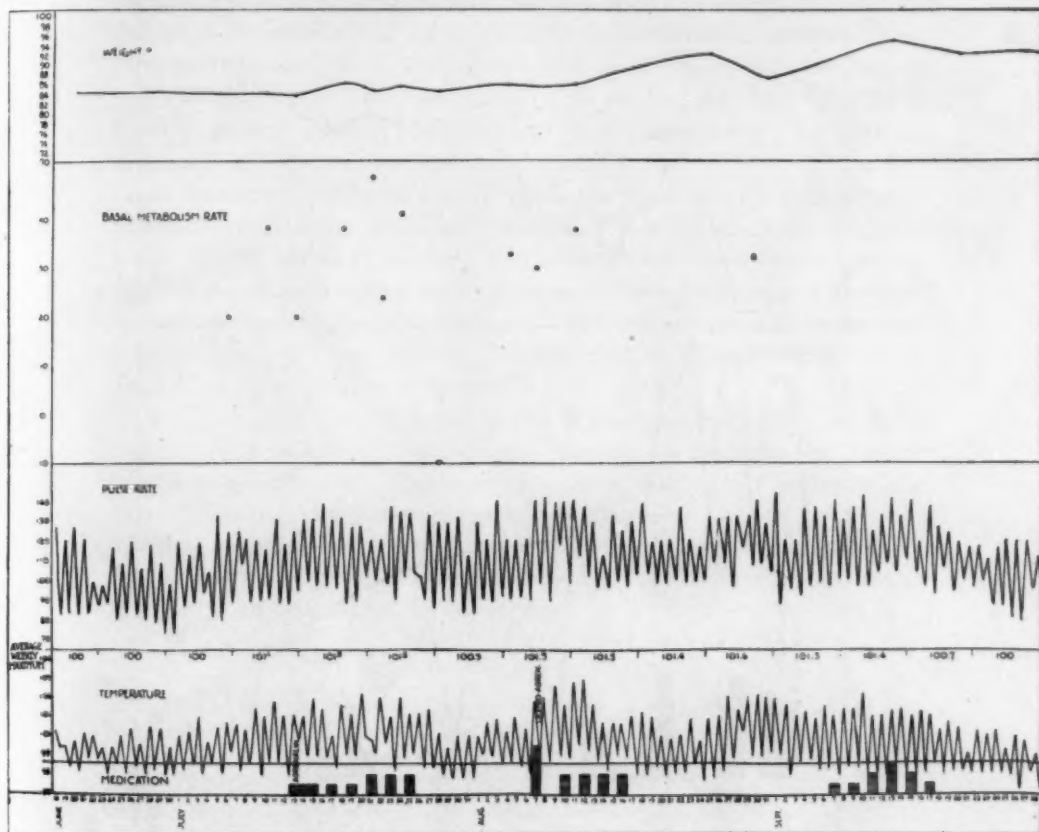


Chart 3.—Clinical record of sister B, who improved on injection of epinephrine.

The examination made when she entered the sanitarium revealed a pulmonary involvement classified as far advanced "B" (Turban III, left III, right II). The sputum was negative; the Wassermann reaction was negative; the tuberculosis complement fixation was +; the hemoglobin content was 75 per cent; the red blood corpuscles numbered 4,050,000 and the leukocytes 11,000 per cubic millimeter. The morning temperature was recorded as 96.4 F. and the pulse rate 100.

The patient was admitted to the Research and Educational Hospital on June 18, 1924, with her twin sister and was observed under identical conditions. The physical examination at admission revealed cavitation in both upper lobes and

soft parenchymal infiltrations throughout both lungs. The weight was 86 pounds (39 Kg.), i. e., 11 pounds (5 Kg.) more than her twin sister's, and her general condition was correspondingly better, owing to her ability to feed herself, the sister A having paralysis of the arm. The temperature and pulse curves were practically identical.

After having been under observation for two weeks, this patient also was inadvertently exposed to sunlight for several hours on July 4 and reacted with an increased temperature, as had the sister. On July 13, 14 and 15, 1 mg. of

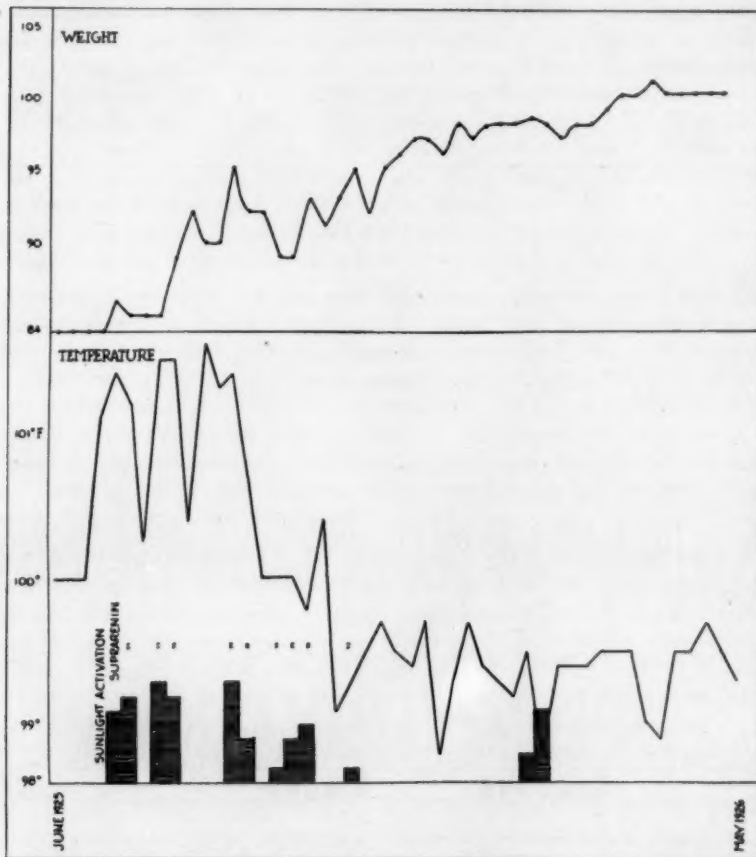


Chart 4.—Condensed chart of year's observation of sister B, showing effect of treatment with epinephrine in tuberculosis activated by an overdose of sunlight.

epinephrine bitartrate (in oil) was given intramuscularly, and similar injections were made on June 17 and 19. On June 21, 23 and 25, 2 mg. were injected and, in addition, calcium lactate was given by mouth. After this course of injections, the temperature receded for five days. The further course of the patient's illness was relatively uneventful. Repeated injections of epinephrine were made, the patient gradually increased in weight and the temperature diminished, but the pulse rate and the basal metabolic rate remained high. The patient was discharged from the hospital in May, 1926, and was still under observation at the time

of writing. She had retained her weight (105 pounds) and the tuberculous process seemed relatively stationary (charts 3 and 4).

Conclusions.—We believe that we may properly conclude that the increase in permeability induced by the pilocarpine injected (moderate dosage in oil) adversely affected the tuberculous process. It brought about increased absorption from the tuberculous foci (indicated by the increases in temperature shortly after the injections, despite the fact that the loss of temperature from the skin must have been accelerated) and with it mobilization of organisms and extension of the disease (terminal meningitis). The objection can be made that the patient was susceptible to cerebral involvement, as she had previously recovered from a solitary cortical tubercle, and that consequently the terminal meningitis represents merely a coincidence.

If increased permeability of tissue is harmful, then diminished permeability of tissue must be beneficial. This seems to be indicated in the clinical course of the twin who received injections of epinephrine. The effects on the temperature of this patient indicate a distinct improvement after each series of injections. The patient gained weight and felt stronger. We may at least conclude that in this patient the injection of epinephrine was not harmful.

It is not our intention in this paper to present clinical material from a therapeutic point of view; we wish merely to establish the experimental possibility that alterations in permeability may influence the clinical picture and that the increase in permeability that we have established as associated with increasing clinical activity may be causative of the clinical status rather than incident to it. The following case histories may be of interest in this connection:

REPORTS OF OTHER CASES

CASE 1.—A young white boy, aged 9, had been ill with Pott's disease for two years. He entered the hospital the first week in January, 1926, with a psoas abscess, which was discharging profusely. For the following three months, he remained under the observation of the orthopedic staff. During this time there was a continued loss of weight with marked anemia and a progressive increase in the temperature to a weekly maximal average of 104 F. (first part of chart 4).

Treatment was commenced on the first of April with a skin burn (Alpine lamp, abdominal exposure, twenty minutes, area 10 by 10 cm., distance 20 cm.). A second and a third exposure were made as indicated in chart 5.

In addition, epinephrine in oil was injected intramuscularly on alternating days, beginning April 9 (five injections). The injections were not continued, because the child was emaciated and the injections caused some pain. Later epinephrine was given by mouth (dosage, 5 drops three times a day).

Sodium citrate was given continuously by mouth from April 11 until the end of May (dosage, 1 Gm. three times a day).

Examination of chart 5 indicates that an improvement commenced about one week after the third period of irradiation of the skin. At about the same time, the discharge lessened and finally ceased two weeks before the patient left the hospital. It was not possible to keep the child for a long time for observation.

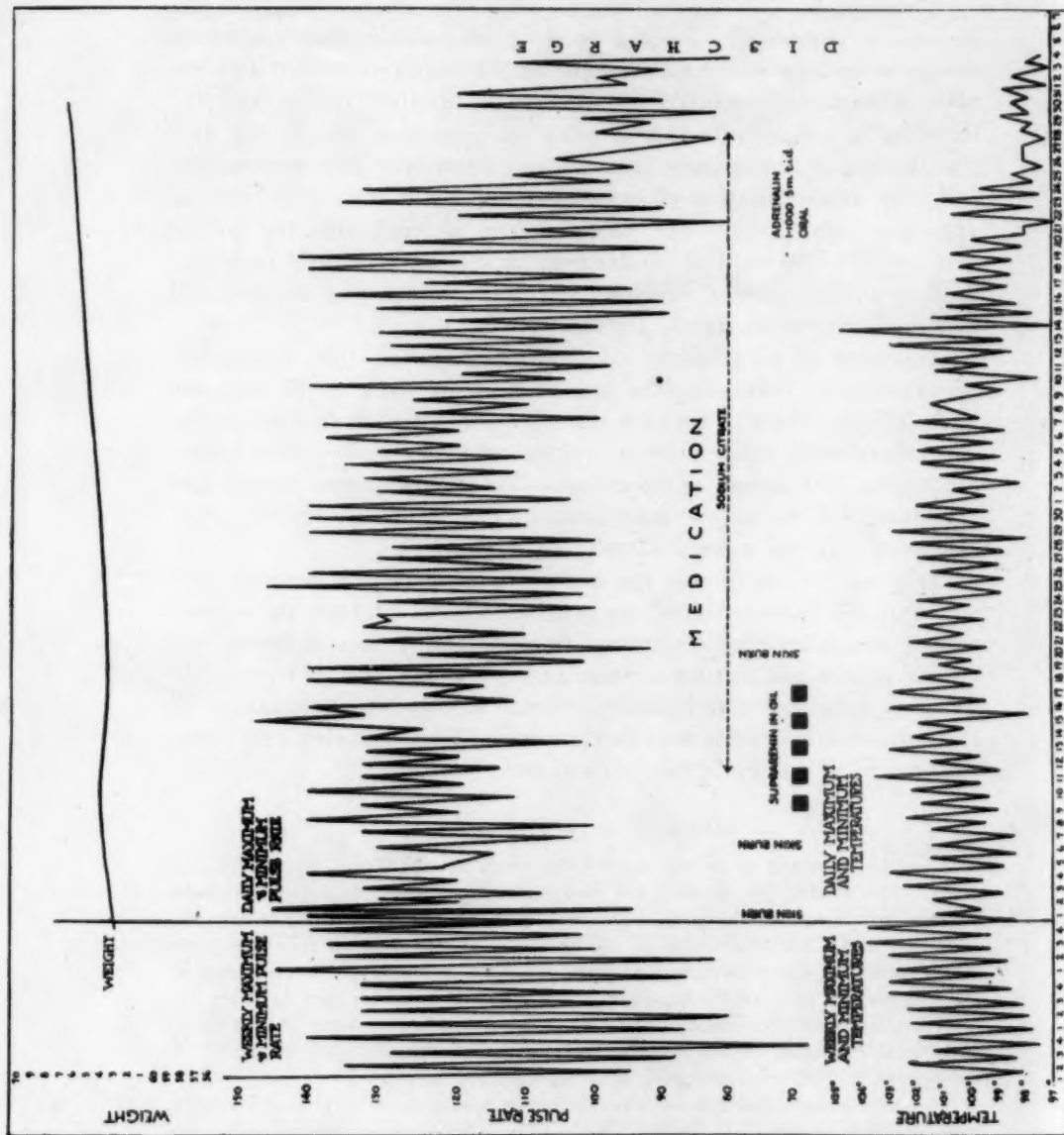


Chart 5.—Effect of treatment with skin burn (Alpine lamp), epinephrine and sodium citrate (case 1).

In this patient, rest in bed and relative immobilization resulted in no improvement during a period of observation of three months. Measures instituted with the view of diminishing capillary permeability were followed by an apparent cessation of the symptoms of activity as far as the psoas abscess and the temperature of the patient were concerned.

CASE 2.—The patient had been ill for at least seven years, beginning with influenza in Germany, where she had collapse therapy of the right lung with subsequent refilling at frequent intervals. She came to America in 1924. She worked hard as a maid and had suffered a breakdown in December, 1924. She was admitted to the Cook County Hospital in December, 1924, and she remained there until Aug. 5, 1925; then she was transferred to the Research Hospital. The maximal and minimal weekly averages of temperature for her stay at the Cook County Hospital are given in chart 6,¹ as well as the daily maximal and minimal temperatures for her stay at the Research Hospital.

Physical examination indicated a far advanced pulmonary tuberculosis with pyopneumothorax of the right side.

The pulse range after admission was somewhat higher than it had been at the Cook County Hospital. No change was made in the patient's routine of life. Ten days after her admission a daily dose of calcium lactate (3 Gm.) was given for three days. There was an immediate effect on the pulse rate, the patient coughed more and had a poor appetite, and four days later the temperature rose to 102.4 F. The sputum was not increased. The pulse rate diminished in the following ten days, but the temperature showed a tendency to increase (marked 1 in the chart).

Epinephrine in oil, in dosage of 1 mg., was now given for five successive days, together with calcium lactate. The patient responded with a marked increase in pulse rate, a rise of temperature and an increase of sputum, was nauseated, coughed more and was sleepless and tired (marked 2 in the chart).

Obviously, the patient responded at least in part vagotonically to the agents that are ordinarily considered sympatheticonic. This is by no means uncommon. We have observed it frequently in animals receiving injections of small doses of epinephrine in oil, and it is, of course, not uncommon in patients in whom the autonomic tonus is so altered that parasympathetic overbalance exists (Guth). The patient returned to the preinjection condition about two weeks after the injections.

On September 29, 5 mg. of epinephrine in oil was given by mouth. An effect was apparent both on the pulse rate and on the temperature (the temperature had increased, however, before the ingestion. (This stage is marked 3 in chart 6.)

A definite cycle of activity took place following October 14. On October 17, the patient received a 5 per cent erythema dose of deep roentgen therapy over the noncollapsed lung. Further doses were given from October 26 to October 27, with evidences of activation following. The patient died December 13.

Anatomic Diagnosis.—Right empyema pleurae and tuberculous cavities in the upper part of the right upper lobe; collapse of the right lung; smaller cavities in the left upper and lower lobes; acinose-nodose tuberculosis of the left lung, and tuberculous bronchopneumonia in the left lower lobe.

Gross Observations at Autopsy.—The thyroid gland weighed 25 Gm. The upper respiratory tract showed large tonsils with deep grooves.

The right pleural cavity was filled with thick pus, and there was complete collapse of the right lung. A cavity, 5 cm. in diameter, was found in the apex of the right lung, communicating with the larger bronchus. There were small areas of bronchopneumonic infiltration in other parts of the right lung. Adhe-

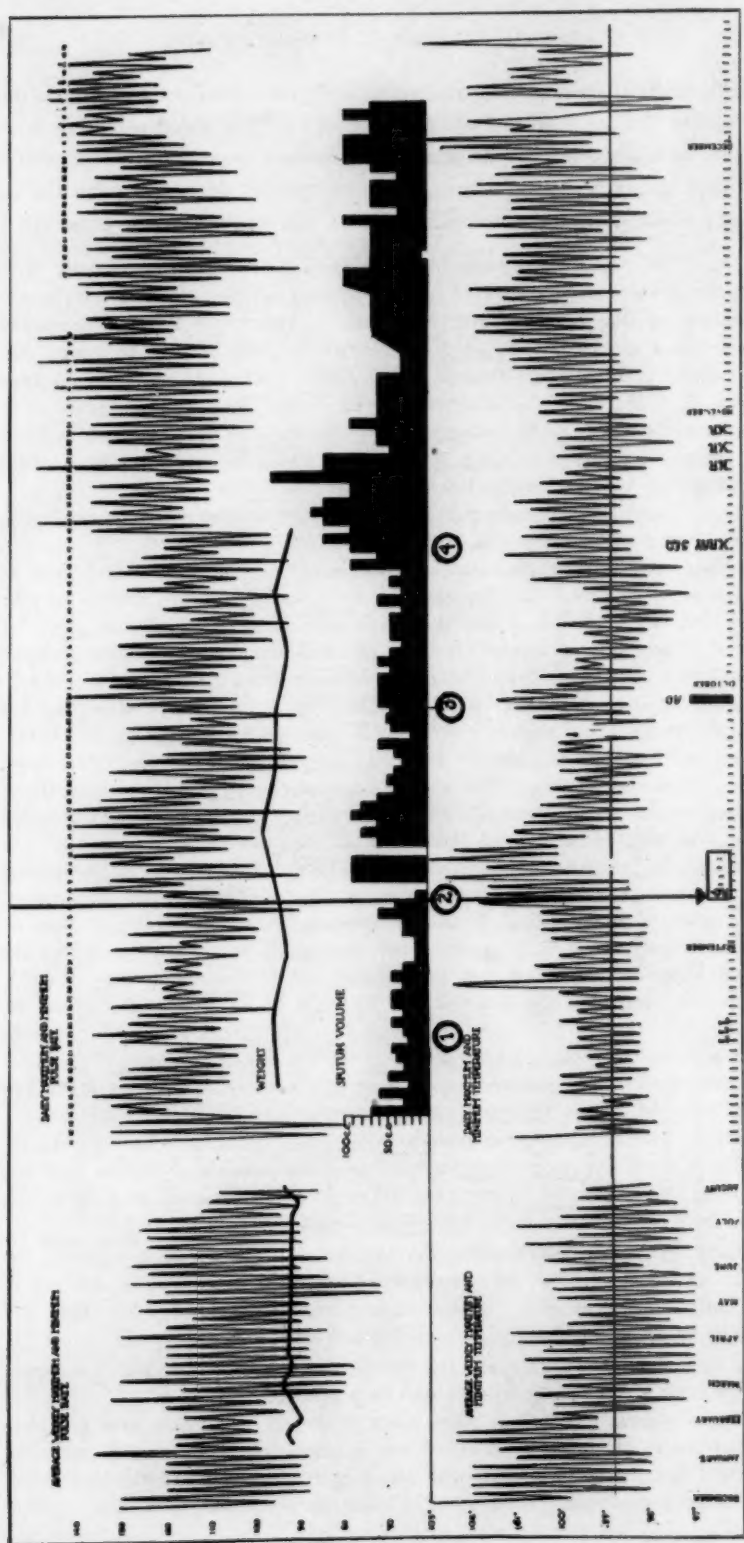


Chart 6.—Clinical record in case 2 (pulmonary tuberculosis with pyopneumothorax of the right side). The patient was treated with calcium-lactate, epinephrine and roentgen ray.

sions were observed about the upper lobe. A cavity, 2.5 cm. in diameter, was found in the upper lobe and another 1.5 cm. in diameter in the upper anterior third of the lower lobe. Acinose tuberculosis appeared in the upper lobe; bronchopneumonic areas in the lower lobe.

The heart weighed 277 Gm. The left ventricle was 12 mm. in diameter, the right ventricle, 6 mm. Small fatty plaques were noted above the aortic valve.

The stomach showed état mammelonné. The intestines showed catarrhal inflammation of the cecum with enlarged follicles, but no tuberculosis. The liver weighed 1,117 Gm. The pancreas weighed 57 Gm. and was 15 cm. long. The spleen weighed 3 Gm. and measured 12 by 3 by 6 cm. The suprarenal glands together weighed 13 Gm. There was little lipid in the cortex, being restricted to a few yellow stripes. The right kidney weighed 140 Gm. and the left 147 Gm. The uterus measured 68 by 40 by 12 mm.

Histologic Observations.—Liver: In the central parts of the acini there was a marked dilatation of the portal capillaries with far advanced atrophy of the liver cells, which often appeared as narrow bands with granules of dark brown pigment and pyknotic nuclei. The liver cells in the periphery of the acini were large and clear, with vesicular nuclei and fine lipid droplets. They were free from pigment. Small groups of cells contained larger fat droplets. Lipoid granules were present in the Kupffer cells. In some capillaries, an accumulation of white blood cells was found.

Spleen: The sinus was of medium width filled with blood. The malpighian bodies were small and without germinative centers; their reticulum cells were often enlarged. Few cells in the pulp contained fat granules. Fine dustlike fat was present in the capsule.

Kidney: Fine fat granules were observed in the basal parts of the epithelial cells of the proximal convoluted tubule. The cells were enlarged, bulging into the lumen. The nuclei were small and vesicular. More fat was found in the distal convoluted tubule. There was capillary hyperemia.

Heart: This organ showed capillary hyperemia, an increased amount of brown pigment about the nuclei of the muscle fibers, distinct striation of the fibers as a rule, and in a few places a granular disintegration of the fibrils.

Suprarenal Glands: There was hyperemia of the zona reticularis. The lipid content of the cortex was distinctly reduced. Larger areas were almost free from fat.

Lung: Upper Lobe: Epithelioid cell tubercles of different size were noted, the larger ones with central caseation. Many giant cells were present. Much fibrosis was seen about the tubercles. The tissue consisted of a homogeneous, poorly stained basement substance that often appeared as blistering bands with a few flat and elongated cells filled with fat granules. Single giant cells and small groups of epithelioid cells were embedded with this scar tissue. The epithelioid cells were distinctly free from fat. So were the giant cells. Fat became visible where central caseation was present, forming a belt of droplets about the necrotic center. In the alveoli around the tuberculous infiltrations, many round cells full of fat were seen.

In using epinephrine, one obviously encounters the fact that it acts on the autonomic nervous apparatus both as a sympatheticotonic and as a vagotonic agent, and particularly in the tuberculous person the probability is rather in favor of the latter. With pituitary, one may anticipate a more certain outcome. We tried this first in combination with epinephrine as well as with a skin burn.

CASE 3.—A young colored man was admitted with a clinical diagnosis of tuberculous peritonitis. The illness had begun six weeks before admission. Swelling of the abdomen had existed for approximately five weeks. The physical examination indicated a pleurisy of the left side with considerable distention of the abdomen with fluid.

After seventeen days' observation, treatment was commenced with the intramuscular injection of pituitary and epinephrine in oil. On January 20, epinephrine was given by mouth, in addition, and later more epinephrine in oil on alternating days. In addition, the patient was burned (ultraviolet dosage similar to that

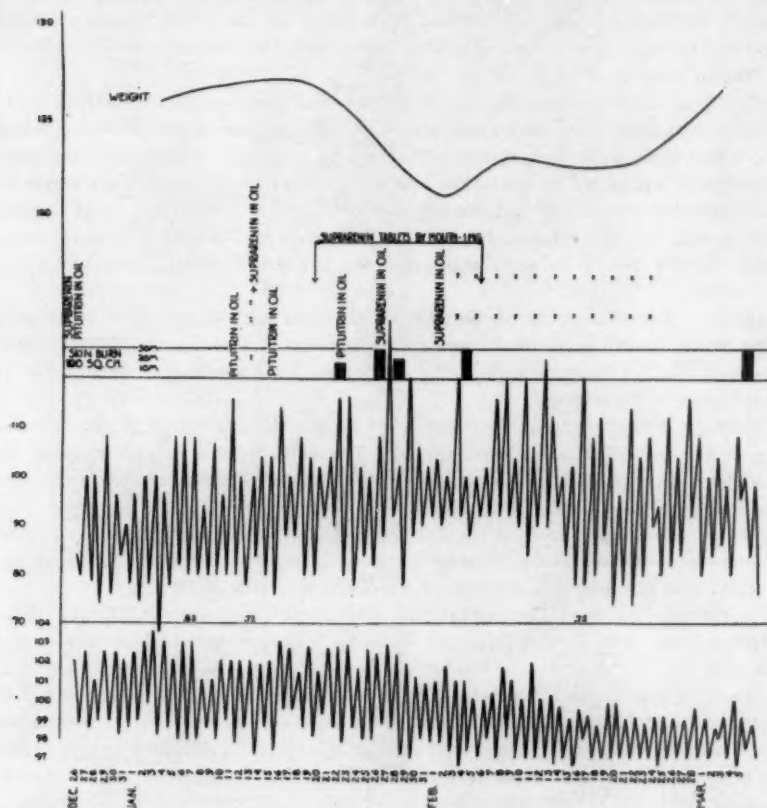


Chart 7.—Clinical record of case 3 (tuberculous peritonitis and pleurisy). Transient clinical improvement is shown.

administered to patient 1) on January 22, 26 and 28, February 4 and March 5. Being heavily pigmented, the patient was resistant to ultraviolet light. The effect of the injections of the drugs on the permeability of the skin capillaries was apparent in a reduction from 0.82 to 0.72.

Following the skin burns, the fluid was promptly absorbed from the peritoneum and the patient's weight diminished 7 pounds (3.2 Kg.). This was followed by a subsequent recovery, without reaccumulation in the peritoneum, and with no apparent further peritoneal discomfort (chart 7).

In this case the patient was by no means cured. Through a misunderstanding, the patient was discharged. He was readmitted April 1, this time with great distention of the abdomen. Because of the discomfort, the abdomen was opened and about 9 pounds (4.1 Kg.) of fluid removed. The peritoneum was found studded with large tubercles. The patient was treated with pituitary and epinephrine in oil and later with epinephrine by mouth. This time there was no apparent effect; the patient was removed from the hospital by relatives, and we have no information concerning the outcome.

CASE 4.—The patient was admitted to the Research and Educational Hospital, May 20, 1926. He was a colored man, aged 24, with a history of typical tuberculous peritonitis of five months' duration. His weight on admission was 130 pounds (59 Kg.).

Physical examination and roentgen examination revealed a far advanced tuberculosis with involvement of the entire right lung, pleurisy of both the right and the left side and tuberculous peritonitis. The blood pressure was 122 systolic and 88 diastolic. On June 22, a thoracentesis was made and 60 cc. of straw-colored fluid was removed. On June 25, approximately 1,500 cc. of fluid was withdrawn. On December 28, another aspiration of the right chest was made and 500 cc. of fluid withdrawn. On December 31 another 500 cc. was withdrawn.

After a short period of observation, the patient was treated with calcium lactate, atropine and small doses of pituitary, the latter preparation practically inert, however. After the preliminary loss of weight associated with the reduction of fluid in the pleural and abdominal cavities, the weight curve was practically stationary. On November 16, three doses of an active pituitary preparation in oil were given daily intramuscularly (indicated by the heavy arrow in chart 8). The pulse rate increased, the temperature declined and the weight fell sharply. A short course of digitalis was given and later the patient was put on a Sippy diet for two weeks. The patient ultimately died, in February. The autopsy was performed by Dr. J. P. Simonds, to whom we are indebted for the report:

Autopsy.—Externally, the body, that of a male, appeared poorly nourished. A lymph gland low down in the neck was palpable. The axillary lymph glands were enlarged. The inguinal lymph glands were somewhat enlarged. On the medial side of Poupart's ligament was an old scar, 5 by 11 mm. The level of the abdomen was about the same as that of the chest.

The fat in the anterior abdominal wall was 5 mm. thick. The intestines were everywhere matted together by dense fibrous adhesions. There were yellowish-white nodules, from 1 mm. to almost 1 cm. in diameter. On section, they were cheesy.

Chest, Right Side: The air escaped when the chest was open. In the anterior mediastinum, in both the upper and the lower parts, were large lymph glands, cheesy on the cut surface. The largest above the diaphragm was 2 cm. in diameter and 0.5 cm. thick. Left Side: The pleural cavity was obliterated by adhesions similar in density to those in the peritoneal cavity. In the lower posterior portion was a cavity between the lung and the chest wall, and the diaphragm was filled with turbid yellowish fluid, in which were many flakes of fibrin. The parietal and visceral pleurae here were covered with a thick layer of yellowish-white exudate. Elsewhere in the pleura there were easily torn fibrous adhesions. Cheesy nodules were found, the largest 7 mm. in diameter. On the right side, the parietal pleura was much thickened and the inner surface was covered with a yellowish exudate. Between the parietal pleura and the right lung was a cavity filled partly with turbid fluid in which were flakes of fibrin. This cavity was partly filled with air. The parietal and visceral pleurae were adherent over the upper lobe. The lower lobes were collapsed and a yellowish exudate covered them.

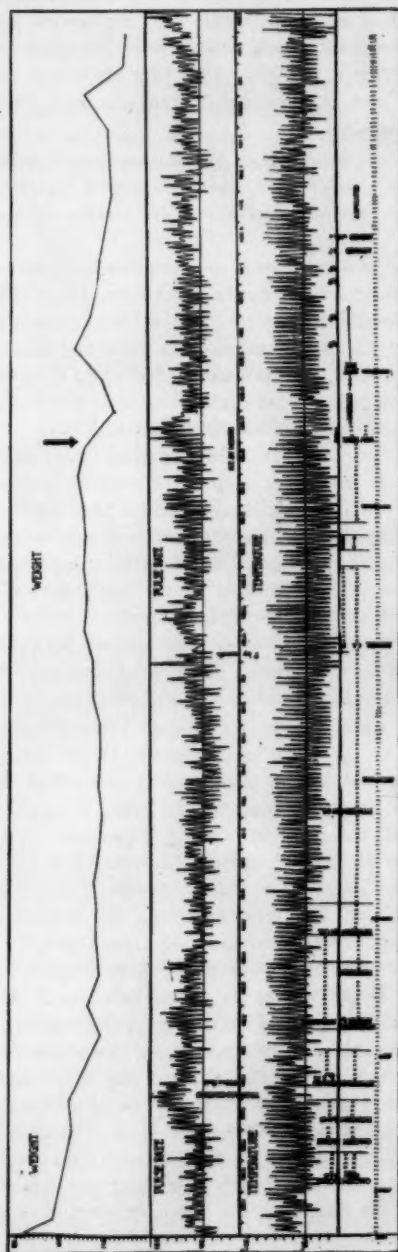


Chart 8.—Clinical record in case 4 tuberculous peritonitis, bilateral pleurisy and far advanced tuberculosis of right lung). The patient was treated with calcium lactate, atropine and small doses of pituitary.

The pericardium contained blood-tinged, clear fluid (50 cc.) and was shining smooth and glistening.

The heart was the size of the owner's right fist. The foramen ovale was closed. The tricuspid orifice admitted five gloved fingertips; the mitral, three. The heart valves were smooth and thin. The myocardium was pale grayish-red and friable; the aorta was smooth throughout.

The left lung, unopened, weighed 630 Gm. It floated in water with the lower lobe downward. The upper lobe crepitated feebly throughout. The lower lobe, upper quarter, crepitated. The remainder was noncrepitant and had the consistency and feel of spleen. The pleural surface was covered with a thick, yellow-white, fibrinous exudate. The cut surface of the upper lobe was grayish red. Frothy fluid escaped on pressure. The cut surface of the lower lobe was also grayish red. Some frothy fluid was squeezed from the upper part. Pieces cut from that portion and from the deeper parts of the remainder of the lobe floated in water.

The right lung crepitated feebly in the lower and upper part of the upper lobe. The remainder of the lung was completely collapsed and airless. The upper part of the upper lobe was adherent to the chest wall. The interlobar fissure was obliterated. The cut surface was grayish and moderately moist (upper lobe). At the hilum were numerous anthracotic lymph glands with large caseous areas. Pieces cut from the upper part of the upper lobe floated. Pieces cut from the lower lobe sank.

The spleen was markedly enlarged and firmly adherent to the diaphragm and also adherent to all other adjacent organs. It weighed from 6 to 90 Gm. There was an accessory spleen about 2 cm. in diameter, in which were several millimeter-sized, cheesy nodules. The cut surface was studded with innumerable yellowish-white, cheesy masses, from 1 mm. to 1 cm. in diameter. There were sharply circumscribed. The cut surface was dry and cheesy. Some of the masses were round; others were lobulated and irregularly confluent.

The liver was large, the capsule everywhere thickened. In places, it was adherent to adjacent organs. It was firmly adherent to the diaphragm. A large part of the capsule was roughly stripped off with removal of the right lung. On the cut surface, some cheesy masses, from 1 to 15 mm. in diameter, were found. Scattered throughout were numerous cavities. The largest was about 2 cm. in diameter. They contained a thick, yellowish-green fluid, and their walls were from 1 to 2 mm. thick. These were yellowish gray. The liver substance was soft and friable. The lobular markings were indistinct. The process had followed the bile duct.

The pancreas showed postmortem changes. The adjacent lymph glands were markedly caseous. The pancreas itself was not involved.

The right suprarenal gland was markedly enlarged. It was almost transformed into a yellowish, cheesy mass. No suprarenal tissue could be made out with certainty. There might have been a small narrow zone of suprarenal tissue of the extremities. The left suprarenal gland was also replaced by a yellowish, cheesy mass.

The stomach was free from ulcerations. The peritoneal surface was studded with cheesy masses.

The right kidney was larger than normal. The capsule stripped easily leaving a smooth surface. There was fetal lobulation. The cortex showed numerous red areas the size of a pin point. The cortex measured from 5 to 7 mm. in thickness. The markings were indistinct. Two separate and distinct pelvises were revealed each opening into its own ureter; the ureters united before entering

the bladder. In one papilla was a millimeter-sized cheesy mass. A larger cheesy mass 6 by 8 mm. was seen in another, and in three papillae the cheesy masses, 2 by 5 mm., were observed. The left kidney was somewhat larger than normal. The capsule stripped easily. The surface was the same as in the right kidney. The cortex was from 5 to 8 mm. thick. The cortical margins were not normally distinct. The bladder showed nothing abnormal.

Anatomic Diagnosis.—Generalized tuberculous peritonitis; tuberculosis of the abdominal, retroperitoneal and mediastinal lymph glands; disseminated tuberculosis of the spleen; tuberculosis of the accessory spleen; tuberculous cholangitis; pyopneumothorax; chronic tuberculous pleurisy, bilateral; compression atelectasis of the lower lobes of both lungs; tuberculosis of the right kidney; double pelvis and urethra of the right kidney; disseminating tuberculosis of the liver; cloudy swelling of the liver and the kidneys; fetal lobulations of the kidney, and tuberculosis of both suprarenal glands.

Histologic Observations.—**Right Lung:** The pleura was covered with a thick layer that in the outer portion was fibrinous and in the deeper parts caseous. The endothelium covering the pleura was completely lost. There was an attempt at organization of the necrotic material resting on the pleura. The pleura itself was thickened, edematous and diffusely infiltrated with lymphocytes, large mononuclears and occasional plasma cells. The blood vessels were widely dilated and had thin walls. The lung tissue in this section showed the alveoli collapsed. There was much pigmentation with coal dust. The bronchi showed considerable desquamation of the epithelium and many contained a finely granular or fibrillar material, in which were scattered polymorphonuclear leukocytes. In the collapsed lung tissue were a number of miliary tubercles.

Liver: Near the center of the section of the liver was a cavity in which was coagulated granular material, some of which was yellow. The inner part of the wall of this cavity was necrotic and caseous. Surrounding this was a narrow zone of fibrosis in which was an occasional tubercle. Elsewhere the liver showed marked postmortem changes. Many of the liver cells still showed considerable fat. Scattered irregularly through the section was a moderate number of miliary tubercles.

Kidney: The section of the kidney showed a large caseous area separated from the remaining kidney substance by a narrow zone of fibroblasts and lymphocytes with an occasional giant cell. Elsewhere there was marked postmortem change in the tubular epithelium and a fairly uniform, moderate increase of connective tissue between the tubules. Many of the tubules in the cortex contained casts. The glomeruli, in general, were richer in cells than normal. In some, the individual capillary loops had lost their identity and the glomerulus appeared as a rather dense cellular mass. None of them showed amyloid. A few glomeruli had been completely transformed in the dense hyaline tissue.

Suprarenal Gland: In this section there was only a small amount of recognizable suprarenal tissue. The remainder was composed of a large caseous mass surrounded by a zone of fibroblasts and lymphocytes with here and there a typical tubercle.

The clinical course is interesting only in that it demonstrates that these large doses of pituitrin were able definitely to depress the temperature curve for approximately one week. The administration was followed by an immediate increase in the pulse rate and consequently we dealt with an added strain on a cardiac musculature already depressed.

The clinical application might therefore seem dubious, but the result seems to offer proof of the theory that the diminished permeability is followed by improvement so far as the temperature is concerned. The loss of weight in this case was undoubtedly due to the transient loss of water.

That pituitary given over a long period need not be harmful in suitable cases seems probable from case 5.

CASE 5.—A colored man, with far advanced pulmonary tuberculosis (large cavity in the left upper lobe), had been transferred from the Cook County Hospital. He had been under observation there from April 10, 1926, to November, 1926. During this time, his weight had declined from 123 to 110 pounds. After being under observation two weeks at the Research and Educational Hospital, he was given three successive doses of pituitary (5 units per dose, in oil, intramuscularly). The temperature diminished, but the pulse increased considerably and there was a loss of weight similar to that observed in patient 4. Later, pituitary was given once a week for five months. During this time, the weight gradually increased and the sputum diminished. For a period of three weeks, large capsules of hydrous wool fat were given. A year after admission, the weight was 140 pounds (63.5 Kg.), and the clinical condition was stationary (chart 9). In view of the fact that the patient had a large left apical cavity, the desirability of collapse was considered and the patient was transferred to the surgical service. He survived the immediate effects of the operation, but died suddenly two days later.

Autopsy.—The body was that of a colored man, aged 35; it was 62 inches in length and weighed 144 pounds (65.3 Kg.).

The left lung had adhesions about the upper portion, and smaller adhesions about the other portions. A large irregular cavity, 9.5 by 7.5 cm. was found in the left upper lobe. The cavity was filled with thin, reddish pus. The wall of the cavity was from 0.5 to 1 mm. thick. It was grayish white, covered on the inside with flat, yellowish-white plaques. In the middle of the posterior wall was a nodule, 3 mm. in diameter, which contained a cavity communicating with the branch of the pulmonary artery. In the right upper lobe were strands of anthracotic scar tissue surrounding firm, cheesy and calcified nodules, 4 mm. in diameter. Single small nodules and areas of granular consolidation were present in the left lobe.

The heart weighed 320 Gm. The left ventricle had a diameter of 13 mm., the right ventricle one of 7 mm. The aorta measured 60 by 42 by 36 mm. Small plaques were observed in the left coronary artery, and larger ones in the arteria abdominalis.

The intestines showed irregular ulcerations extending down to the muscularis and with slightly thickened undermined edges in the cecum and lower parts of the colon ascendens. There were adhesions about the appendix, which was dilated and contained near its origin a whitish nodule, 5 mm. in diameter.

The liver weighed 1,440 Gm., and showed distinct markings. The pancreas weighed 100 Gm.; the spleen, 120 Gm. The left suprarenal gland presented a light yellow cortex. The right kidney weighed 160 Gm., the left, 150 Gm. The capsule was adherent. The surface was studded with small irregular, grayish-brown nodules. A gray nodule the size of a pinhead was present in the medulla of the left kidney. The brain weighed 1,370 Gm. Besides these changes, a recent thoracoplastic operative wound was observed, with resections of half of the first left rib.

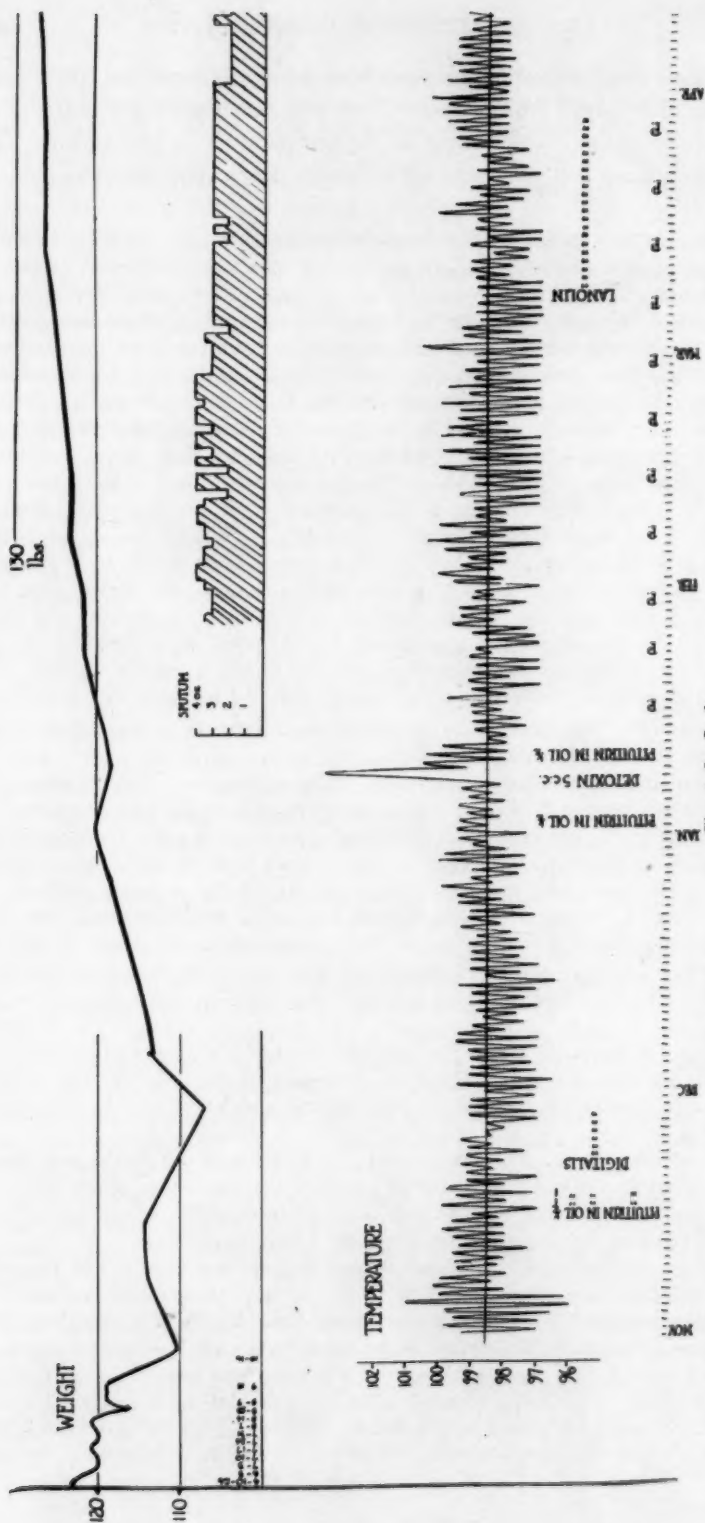


Chart 9—Left

Chart 9.—Clinical record in case 5 (far advanced pulmonary tuberculosis). The patient was treated with pituitary.

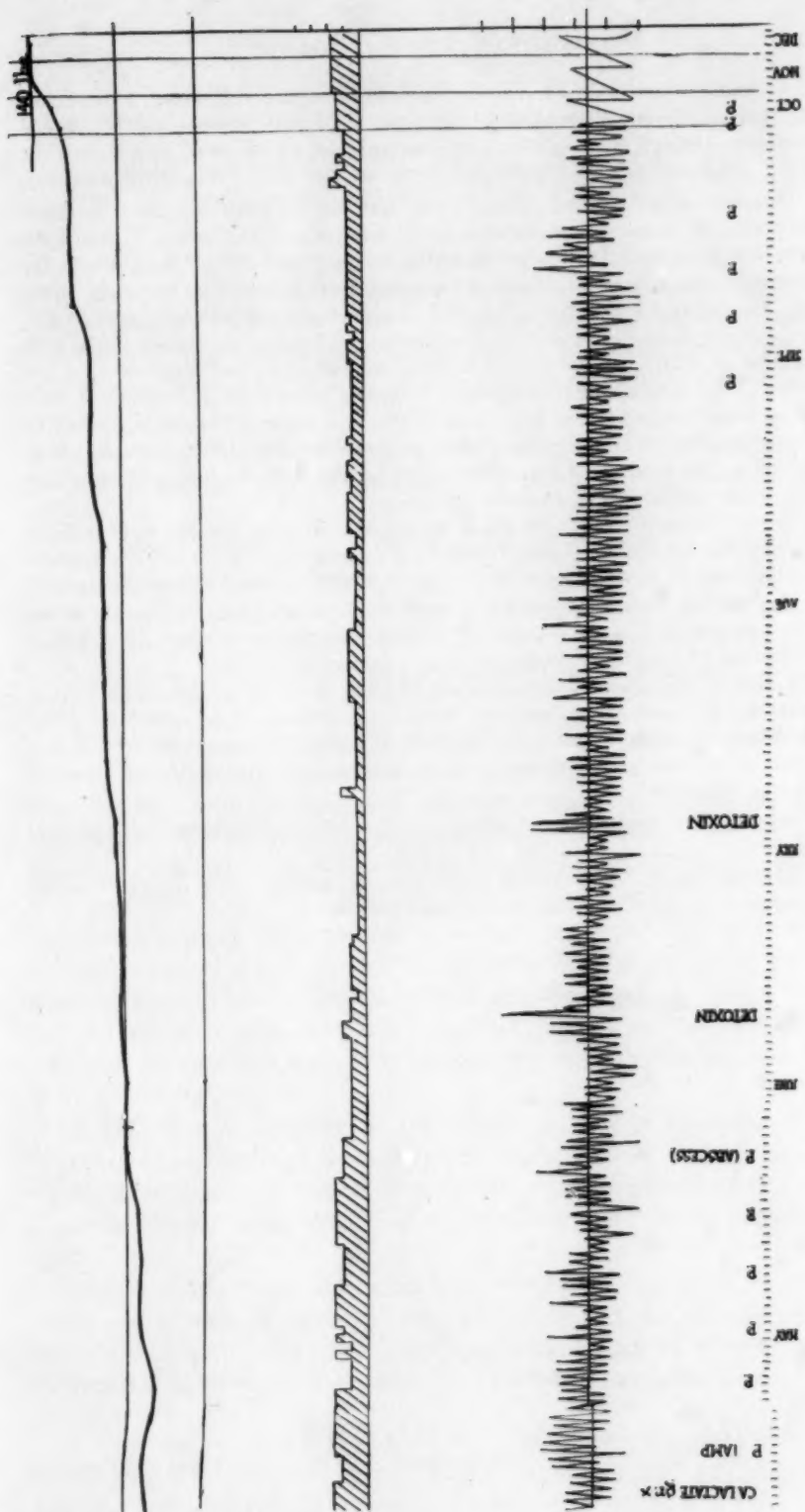


Chart 9—Right

Anatomic Diagnosis.—Ulcerative tuberculosis of the left upper lobe of the lung; chronic fibrous tuberculosis of the right upper lobe; bronchitis and bronchial pneumonia of the left lower lobe; fatty degeneration of the liver; cloudy swelling of the kidneys; ulcerative typhlitis; edema of the brain; recent thoracoplasty.

Histologic Observations.—Lung: The wall of the cavity in the left upper lobe consisted of cellular granulation tissue with dilated capillaries. Toward the lumen the granulation tissue gradually passed over into cheesy masses. In the granulation tissue were many typical Langhans giant cells and a few young tubercles. Groups of foreign body giant cells contained peculiar calcified round bodies. In the outer portion, the wall was composed of fibrillar connective tissue with glandlike structure. Some of the arteries showed a marked thickening of the intima. In the left upper lobe, single tubercles were observed, composed of a cheesy center surrounded by dense scar tissue, with much anthracotic pigment. In the surrounding parts a few giant cells were assembled but there were no young tubercles. The lung tissue adjacent to the tubercles with the fibrous capsule contained many accumulations of lymphocytes.

Lymph Glands: The lymph glands presented a diffusely calcified mass enclosed in a thin capsule of fibrous tissue. Near the capsule was a giant cell containing a calcified body. The other parts of the gland were hyperemic with much pigment.

Liver: The liver cells contained small fat droplets. Near the center of the acini were granules of dark brown pigment besides the fat droplets. There were infiltrations of round cells in the periportal connective tissue.

Kidney: The kidneys showed circumscribed areas of atrophy with hyaline glomeruli and round-cell infiltration. There was swelling of the epithelium of the convoluted tubules in the parts between the atrophic areas. Much fat was present in the lining epithelium of the ascending part of Henle's loops and the collecting tubules.

Spleen: The spleen showed fibrosis of the pulp, and small follicles without centers.

Thyroid Gland: The thyroid gland revealed medium-sized vesicles lined by flat epithelium and filled with homogeneous colloid.

VIII. THE INTRACUTANEOUS REACTIONS TO INJECTION OF PHARMACOLOGIC SUBSTANCES DURING CHILL AND FEVER

In order to determine in some measure the extreme effects of vascular changes on the picture obtained when the intracutaneous pharmacologic tests are made, we examined the reaction in patients during the course of malarial inoculation, the determination being made before inoculation, during the time of chill and during the period of perspiration.

In the chart, we have illustrated the relative sizes of the wheals and the flares at the sites of injection of epinephrine, morphine, thyroxin and caffeine.

The wheal at the site of the injection of epinephrine during the time of the chill was somewhat reduced (on an average, from 10 to 15 per cent), while the flare was much more reduced. This was particularly apparent in patient 2. During sweating, the wheal regained its original size, and in two patients, the flare became much larger than under normal conditions.

With morphine, too, during chilling, there was an apparent reduction of both the wheal and the flare, except in patient 4.

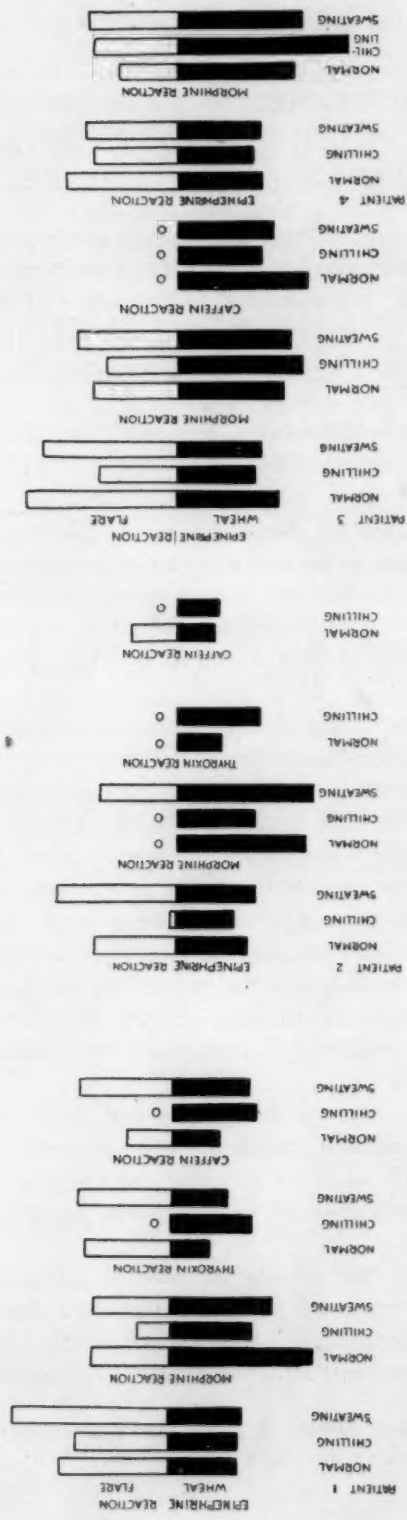
With thyroxin, the wheal was increased during the time of the chill in two patients, but no flare appeared. With caffeine, there was an increase in the size of the wheal during chilling in patient 1, but a reduction in patient 3, so that the results were inconclusive.

During chilling, the autonomic orientation is such¹ that the skin is distinctly sympathetic, while the visceral area is parasympathetic (these terms being used here to designate the state of the capillary bed). During chilling, too, epinephrine is being thrown into the circulation in increased amounts and apparently it accentuates the constriction manifest in the peripheral vessels.

A reduction in the size of the wheals and flares at the sites of injection of epinephrine and morphine made evident during chilling might, therefore, justify us if we interpret reduced size of wheals and flares in general as indicative of an increased sympathetic peripheral tonus.

On the other hand, the wheals at the sites of injection of thyroxin and of caffeine appeared somewhat increased during chilling in two patients, giving further evidence that the effects of thyroxin and caffeine are in direct contrast with the effect of epinephrine.

1. Petersen, W. F., and Müller, E. F.: The Splanchnoperipheral Balance During Chill and Fever, *Arch. Int. Med.* **40**:575, 1927.



A comparison of the sizes of the wheals and the flares at the sites of injection of the pharmacologic substances during malarial inoculation with their sizes under normal conditions.

IX. DISCUSSION AND DEDUCTION

CONTENTS

General Considerations

- Study of the Individual Constitution
- Views of Kraus, Bauer, Verschuer and Others

The Slender (Asthenic) Versus the Heavy (Pyknic) Person

- The Sympatheticotonic Versus the Vagotonic Type
- The Thyroid Type

Autonomic Equilibrium

- Daniélopou's Concept of Vegetative Tonus
- Autonomic Equilibration and Increasing Amplitude of Response
- Schilf's View of Autonomic Antagonists

The Chemical Equilibrium

- Rôle of Calcium and Potassium and the H-Ion Concentration
- Confusion of the Terminology Involved
- Clinical Grouping of Vagotonic and Sympatheticotonic Persons
- Rôle of Cholesterol

The Skin

- Its Autonomic Importance
- Local Resistance
- Herpes and the Splanchnoperipheral Balance
- Respiratory Tract
- Gastro-Intestinal Tract and Change of Temperature

Exophthalmic Goiter

The Nervous Patient

Glaucoma

Tuberculosis

- Constitution
- The Autonomic Status
- The Vascular Reaction to Tuberculin
- Correlations Based on Clinical Classifications, Weight Curve, Clinical Prognosis and Fatalities
- Calcium
- Cholesterol
- Reactivity of the Skin
- Leukocytic Reaction
- Therapeutic Considerations

GENERAL CONSIDERATIONS

In the preceding group of papers, an effort has been made to correlate a number of measurable biologic reactions observed in normal persons and in patients, with each other, with clinical symptoms and with resistance to an infectious disease, i.e., tuberculosis.

In making the tests, we have sought to employ such as might presumably give information concerning the vegetative status of the individual, more particularly the status of the vascular system and the

epidermis. We have sought, furthermore, to determine whether such a vegetative or autonomic status is related to the genotype or whether it is conditional (paratype, and therefore modified by preexisting and latent infection).

Incidentally, we have sought to determine what alterations in the tests that we have employed are indicative of increased or decreased resistance to tuberculosis and what therapeutic deductions might be drawn from such indications.

In view of these particular interests, we cannot avoid a preliminary discussion of certain concepts concerning the vegetative status of the organism and the relation to the constitution in its widest sense.

Study of the Individual Constitution.—It is perhaps a natural swing of the cycle that is bringing medical interest back to an analysis of constitution and conditional reactivity. The triumph of the "era of specific etiology" had completely overwhelmed every thought of constitutional differences in reactivity. Obvious clinical experience was discredited and discarded when in conflict with experimental results from the animal laboratory. Correction has followed, however, because of the obvious fallacy of the underlying method. Precise clinical observation and animal experimentation brought incontrovertible evidence that neither in man nor in animals do like reactions necessarily follow like insults. Even the physiologists and the pharmacologists have recognized that normal animals in deep anesthesia offer a test object totally different from sick patients.

Recognition of the importance of differences in the host has come from the epidemiologist, as well. Thus there are differences in reactivity of the skin and the mucous membranes, respiratory, as well as gastro-intestinal, which determine in a large measure one's liability to infection, as Arnold¹ has recently pointed out.

The scientific study of the individual constitution has been under way from two important nonmedical sides. The earlier anthropologist sought to formulate and define racial groups. More recent studies have been broader and have sought to establish general types irrespective of racial grouping. To this comes an added impulse through the modern study of heredity.

Naturally, physicians have sought to make use of these two lines of approach and have applied them particularly to noninfectious diseases—in which "heredity" and "constitution" have never quite been denied. But emphasis on anthropologic and genetic phases savors too much of predetermination to be wholly acceptable to the medical observer. The conditional factors of environment, of tissue experience,

1. Arnold, Lloyd: J. Hyg. 29:82, 1929.

of preceding infection, of food, of light, of autonomic training (particularly of the skin), of climate—these must be of equal importance in variable susceptibility to infection, and resistance to one already established. However, many fruitful clinical observations and correlations have taken origin from these two sources. The literature is too large to be discussed, but a recent paper of Draper² and his co-workers is illustrative.

Views of Kraus, Bauer, Verschuer, and Others.—"Constitution" as a factor in the disposition to disease means different things to different investigators, depending on their particular interests.

We may, for instance, with Leo Loeb regard constitution as a synthesis and vital unification—the "individuality differential"—a view held by Martins and his school, as well; or go to the opposite extreme with Draper and examine everything from a purely anthropometric point of view. Bauer,³ on the other hand, discounted the value of the various anthropometric "indices" of this school, but nevertheless limited the term to the "genotype." Pfaundler stressed the importance of environmental (conditional) forces, i. e., the "paratype."

Many physicians have sought to group persons according to the presumptive reactivity of their glands of internal secretion and speak of the "hypophyseal," the "thyroid," or the "adrenal," type. Stern worked out a rather elaborate "glandular formula" and Pende⁴ theorized considerably in this direction. Of course, such a classification is attractive because it makes more easy the correlation of genotype and phenotype, the endocrine glands acting, presumably, in the modification of the inherited structure. With definite evidence of nervous control of the suprarenal (Cannon) and thyroid glands (Ascher⁵), the circles of biologic control become ever more intricate.

Kraus⁶ and his school, primarily clinical in orientation, stressed the idea of "personality," the term "Syzygiologie" having been coined for the new field.

The novelty of this point of view lies in the fact that it emphasizes the periphery of the organism, the region in which the metabolic processes are going on, and particularly the exchange between the cell and its environment, i. e., the membrane of the cell. As components of this system are to be regarded all factors that play into this intricate

2. Draper, G.; Allen, Grace, and Spock, Jane: Studies in Human Constitution, *Clinical Genetics*, J. A. M. A. **92**:2149 (June 29) 1929.

3. Bauer, J.: *Klin. Wchnschr.* **8**:145, 1929; *Ann. Int. Med.* **2**:127, 1928.

4. Pende, Nicola: *Constitutional Inadequacies*, Philadelphia, Lea & Febiger, 1928.

5. Asher, L., and Pfluger, O.: *Klin. Wchnschr.* **6**:1614, 1927.

6. Kraus, F.: *Allgemeine und spezielle Pathologie der Person*, Leipzig, Georg Thieme, 1926, pt. 1.

exchange, either accelerating or inhibiting it, as for instance, water, the colloid electrolytes, salts, combinations of cations, the buffer system, hormones, definite endogenous and exogenous irritants and poisons, as well as the catalysts.

The local and transient balance of this intricate mechanism is not determined only by the degree, the direction and the rapidity of the specific cell functions, but also by the degree and directions of the vegetative nervous irritability. The vegetative nervous system has the function of regulation—regulation in the sense that it determines to a large degree the distribution of the electrolyte reserves from one place to another.

In the logical development of this idea, Kraus came to the conception of a phylogenetically long established "Tiefen-person," that individualism of the most vital and most profound sort, a vital component of the constitutionally and primarily ordained protoplasm. This fundamental individualism is to be placed in contrast with the centrally organized and much younger cortical personality.

One of the great advances which lies in this concept of the constitution is, we believe, the fact that it emphasizes the impossibility of trying to coordinate isolated observations on both nervous systems (vegetative and central) without a proper regard for all the other factors of the vegetative apparatus. On the other hand, it is of use in the proper evaluation of the vegetative nervous system for all of our clinical problems. We shall refer repeatedly to the general idea.

Daniélopou⁷ also stressed the importance of the periphery, i. e., the terminal organ as the site at which the basic orientation of the individual is determined.

Perhaps, the simplest and most useful of medical points of view of constitution is that of von Verschuer,⁸ who defined it merely as "the relative (constitutional) status in the terms of resistance," stressing, nevertheless, that constitution (= Körperverfassung of Tandler = status,) is an organically fixed condition.

Bauer emphasized the importance of constitution in differentiating a group of biologically inferior persons—extreme variants from the normal—in adaptability, in vitality and in resistance. This, too, might seem a most useful concept for the physician.

He was content for practical purposes to group persons as:

Slender	Normal	Heavy
(Dolicho, or asthenic type with small heart)	(Normotype)	(Brachy, or pyknic type)

7. Daniélopou, D.: Presse méd. **31**:649, 1923.

8. Von Verschuer, O.: Klin. Wchnschr. **6**:769, 1928.

The French have always associated the first group with lessened resistance to pulmonary infections; the latter group with gout, rheumatism, diabetes and arteriosclerosis.

Sigaud made extensive use of the type terms muscular, respiratory, digestive and cerebral. Kretschmer added the study of character in relation to constitution, the conscious reactivity being obviously a part of the general constitutional makeup. To these and related classifications must be added those concerned chiefly with the functional status of the endocrine glands and finally the grouping of persons as primarily sympatheticonic or vagotonic.

While we cannot review the recent contribution of Brown⁹ at great length, we cannot but quote the pertinent conclusions that he has drawn from an elaborate and most convincing series of animal experiments that illustrate certain phases of constitutional resistance to disease. Brown wrote:

The elementary conception of constitutional variation and its relation to disease which I have attempted to outline involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions. One need not know the function of a single organ in order to show that persons differ from each other in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic microorganisms. It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by the changing conditions of life and that these changes in organic constitution are accompanied by variations in chemical constitution, all of which may be confined within the usual limits of normal, for they are normal. It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity.

In studying our material, we have disregarded all anthropometric factors and have used only the grouping of slender, normal and heavy, as based on the weight/length ratio.

THE SLENDER (ASTHENIC) VERSUS THE HEAVY PERSON

It will be recalled that our two extremes based on such a classification showed, in general, the conditions set forth in table 1.

Does such a classification have any necessary relation to the concept of "sympatheticonic type" or "vagotonic type?"

The Sympathetic Versus the Vagotonic Type.—When we examine the ten persons with the extreme "sympatheticonic" reactions and the

9. Brown, Wade H.: Constitutional Variation and Susceptibility to Disease, Arch. Int. Med. 44:625 (Nov.) 1929

ten with the extreme "vagotonic" reactions to epinephrine, as determined on the basis of the systolic reaction, we find the characteristics to be as shown in table 2. While the two classifications are by no means identical, we see that in both we deal with slender persons who have a

TABLE 1.—*Characteristics of Slender Persons and Heavy Persons of Extreme Type*

	Slender * (Weight/Length Ratio 1.87)	Heavy † (Weight/Length Ratio 2.32)
Capillary permeability	0.63 greater	0.57
K/Ca ratio	1.81 lower	2.09
Sugar	60.50 lower	73.80
Basal metabolic rate.....	+10.00 greater	+7.00
Muscle reaction	2.38 greater irritability	3.48
Epinephrine pulse pressure.....	+12 increased effect	+8.00
CO ₂ -combining power	+58.5 slightly more alkaline	54.4
Cholesterol	210 lower	225
Reactivity of skin		
Resistance of skin to electric current	0.66 higher	0.28
Reaction to ice	21 longer	19
Kromayer light erythema time..	2.21 longer	2
Epinephrine wheal	18.8 smaller	20
Morphine flare	14.8 smaller	15.8
Thyroxin wheal	12.2 larger	11
Thyroxin flare	4.8 larger	3.2
Caffein wheal	19.2 larger	18
Caffein flare	2.8 larger	2.4

* Microsplanchnic type: phthisic habitus; asthenic habitus; linear type of Stockard; Pende presupposes an increase in basal metabolism; predominantly "sympatheticotonic."

† Megalosplanchnic type: "apoplectic" constitution; pyknic type of Kretschmer; lateral type of Stockard; Pende presupposes increased cholesterol, increased potassium, relative alkalosis and chloride retention; predominantly "vagotonic."

TABLE 2.—*Characteristics of Sympatheticotonic Persons and Vagotonic Persons of Extreme Type*

	Sympatheticotonic Group	Vagotonic Group
Capillary permeability *	60.1 increased	64.5
K/Ca ratio *	1.74 lower	2.04
Basal metabolic rate.....	+10.4 equal	+10.9
Muscle reaction	4 increased	2.3
Epinephrine pulse pressure *.....	+21.4 higher	-1.3
CO ₂ -combining power	54.6 lower	57.7
Cholesterol *	209 lower	218
Reactivity of skin		
Resistance of skin to electric current..	0.41 equal	0.43
Reaction to ice *.....	23 longer	20
Kromayer light erythema time.....	1.72 shorter	1.96
Epinephrine wheal *	19.4 smaller	20
Epinephrine flare	9.4 larger	8.3
Thyroxin wheal *	12 larger	11.4
Thyroxin flare *	4 larger	3.2
Caffein wheal *	21 larger	19.2
Caffein flare *	2.6 larger	2.4

* The reactions indicated by (*) are identical in direction in both the "slender" and the "sympatheticotonic" groups.

low K/Ca ratio, an increased vascular reaction to epinephrine, lower cholesterol, somewhat less reaction of the skin to epinephrine, and a greater reaction of the skin to thyroxin and caffein.

The "slender" person in contradistinction to the heavy person has, furthermore, an increased basal metabolic rate, a more irritable musculature with a slightly lower CO₂-combining power of the serum, higher

resistance of the skin to electric current and a longer Kromayer light reaction time.

The "sympatheticotonic" person in contradistinction to the "vago-tonic" person has no difference in the basal metabolic rate, less muscular irritability and a lower CO_2 -combining power, no difference in resistance of the skin to electric current and a slightly slower Kromayer light reaction time. The blood pressure is lower.

The Thyroid Type.—If we now compare the extreme "thyroid" type, we also have a slender person (ratio 201) with increased capillary permeability (ratio 72) and increased basal metabolic rate (+ 48), no change in the K/Ca ratio, but an increase in the total serum calcium and potassium; the skin blister time is shortened, the ice reaction time is rapid, the resistance of the skin to electric current is low and the epinephine wheal is small.

Pende¹⁰ assumed that the sympathetic type is characterized by a state of defense and aggression (raising of blood pressure and pulse rate, glycogenolysis, etc.) the parasympathetic type by emphasis on intestinal and reproductive phases (glycogen formation, congestion of sex organs, etc.).

Goldstein, too, stressed the general catabolism, irritability and aggressiveness of the sympatheticotonic status as contrasted with the euphoria and hypomaniacal status of the vagotonic psychopathic person.

In this country Cannon, in particular, has studied the sympathetic nervous apparatus and recently demonstrated the nonvital character of these nervous impulses. Even the medullary chromophil tissue of the suprarenal glands in contrast with the cortical portions of the glands—is apparently without vital importance. After bilateral sympathectomy, emotional excitement does not cause erection of hairs, consistent increase of blood sugar, polycythemia, relative increase in mononuclear cells or marked rise of arterial blood pressure. Sympathectomized animals are sensitive to cold, and having lost the means of conserving heat, they lose heat more rapidly than normal animals. The basal metabolism usually falls somewhat after sympathectomy, especially after the cervical portion is excised. Though seemingly unessential under "normal conditions," it is of great service at times of critical emergencies when it adjusts the internal organs of the body for the use of the mechanisms responding to external exigencies.

The experiments of Cannon¹¹ and his co-workers are of particular importance because they demonstrate that the humoral factors (particularly the chemical) of integration of vegetative phenomena, after all,

10. Pende, N.: *Riforma med. Naples* **41**:241, 1925.

11. Cannon, W. B.: *Science* **69**:502, 1929.

represent the older and underlying mechanism and must be considered in all of our medical problems, the nervous system being merely the more recent and less essential factor. As such, however, it may be the first to become disorganized and the first to give rise to clinical symptoms.

AUTONOMIC EQUILIBRIUM

The original concept of Eppinger and Hess of sympathicotonic and vagotonic types has unfortunately been so impressed on the medical mind that more modern developments dealing with the autonomic status of the individual have found but slow acceptance.¹² It should be understood, as Ascher has so clearly stated, that the individual cells of the body are functionally distinct individuals, regulating their existence primarily through chemical means (this involves ionic, molecular, hormone and catalytic processes) and secondly, through nerve impulses, either central or vegetative.

Daniélopolu's Concept of Vegetative Tonus.—Daniélopolu¹³ postulated three laws concerning reactions of the autonomic response which have an important bearing on the sympathicotonic and vagotonic conception.

In the first place, substances that influence one factor also influence the other; i. e., they are amphotropic. The evidence for this has been accumulating for many years, and the literature has been reviewed repeatedly.¹⁴

With eye pressure, Daniélopolu demonstrated that the impulses proceed along two pathways, along the parasympathetic to the heart and along the sympathetic to the gastro-intestinal tract. Daniélopolu concluded that the vegetative tonus is maintained by amphotropic factors: one, peripheral and humoral, the other centrifugal, from the sympathetic and parasympathetic centers. When the tonus of one side is increased, the other automatically follows.

In clinical medicine, we frequently see, however, an apparent overbalance of the one system. Daniélopolu believed that the preponderance depends on the intensity of the impulses. In pharmacologic experiments, we know the importance of the size of the dose of the autonomic drugs. The effect on an organ depends on the general vegetative status of the entire organism, i. e., a minimal dose of epinephrine, which in the normal person results in parasympathetic stimulation (i. e., slowing heart rhythm and lowering of the blood pressure) causes increased blood pressure and pulse rate in the sympathicotonic person; on the other

12. Editorial, Constitutional Vagotonia, J. A. M. A. **93**:1387 (Nov. 2) 1929.

13. Daniélopolu, D.: Klin. Wchnschr. **7**:1748, 1928.

14. Pick, E. P.: Arch. f. Physiol. **79**:183, 1920; Deutsche Ztschr. f. Nervenhe. **106**:238, 1928. Sollman, Torald: Physiol. Rev. **2**:479, 1922.

hand, the dose which in the normal person causes increased blood pressure and pulse elicits a parasympathetic effect in the vagotonic person. These so-called paradoxical or inverted effects are, of course, well known. Finally, Danielopolu postulated a circular mechanism, the diagrammatic presentation of which we have reproduced.

Autonomic Equilibration and Increasing Amplitude of Response.—

At this point, we should like to illustrate another fundamental phenomenon constantly met with in the study of autonomic regulation: first, the constant manifestation of the effort of the cell and the organ and the organism as a whole to maintain an equilibrium, disturbances of the balance being always followed by rhythmic and wavelike fluctuations in a direction opposite to the original change in status; second, the frequent manifestation of a progressive increase in amplitude in such rhythmic fluctuations following single impulses. We give charts for three typical experiments. The first shows the peripheral leukocytic fluctuations following bulbus pressure in the dog; the second, following irradiation of the skin. The third shows chemical fluctuations following a bacterial insult.

In a normal dog, a lymph fistula was made under local anesthesia. After reaction, bulbus pressure was maintained for seven minutes at the time indicated in chart 2. Peripheral leukocyte counts were made at frequent intervals, with determinations of lymph concentration, sugar, calcium and erepsin. The leukocyte count which reveals the fluctuations in the peripheral tonus (dilatation of vessels—leukocytosis; contraction, stasis, leukopenia) clearly indicates the rhythmic fluctuations of increasing amplitude initiated by this stimulus.

An almost identical picture is illustrated in chart 3. This dog had an exposure for seven and a half minutes to ultraviolet light applied over the abdomen, following recovery from incannulation of the thoracic duct under local anesthesia. It will be observed that the leukocyte curves show minor oscillations of increasing amplitude, with three chief periods of leukocytosis, the first 30 minutes, the second 75 minutes and the third 130 minutes, after the exposure. Calcium diminution occurs at approximately the same intervals.

In chart 4 we are able to illustrate an even more convincing picture with corresponding calcium fluctuations. In this case we deal with a bacterial insult. A pregnant dog was operated on under local anesthesia and an incannulation of the thoracic duct was made. After a period of observation following the operation, the continuous intravenous injection of a dilute suspension of *Bacillus coli* in saline solution commenced at 11:25 (first arrow on chart).

The curves at the top of the chart indicate the sugar level and the double line the K/Ca ratio (calcium level in black columns; potassium, in white columns).

The second group of curves indicate the rectal temperature and the volume of urine; the third, the lymph protein volume, the globulin per cent (in black) and the leukocyte curve. Inasmuch as the volume was sufficient to permit chemical analysis in five-minute samples, the actual fluctuation in the K/Ca ratio more accurately reflects the changes that occur in the tissues than has been possible in most of our other experiments.

It will be observed that the initial reaction was a slight increase in the calcium. A second and larger increase followed, reaching a maximum approximately sixty

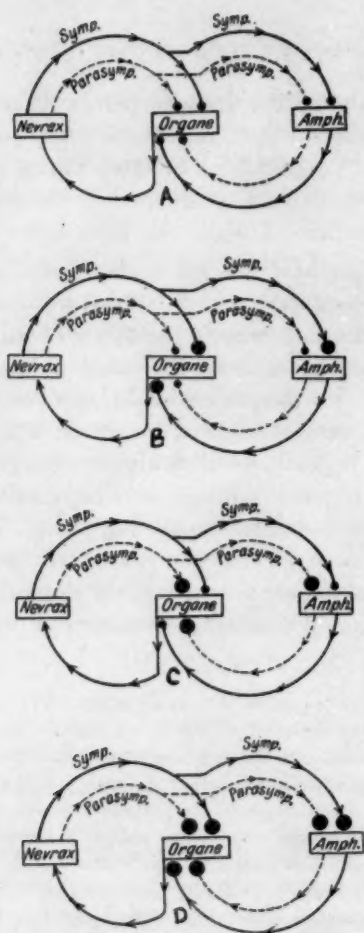


Chart 1.—Amphotropic circular mechanism of the autonomic tonus and its variations (from Danielopolu, D.: *Klin. Wehnschr.* 7:1748, 1928). Diagram A indicates the normal status, i. e., equal sympathetic and parasympathetic amphotropism indicated by the equal size of the black dots.

Two factors are outlined: the peripheral amphotropic humoral factor (involving calcium, potassium, epinephrine, choline, pituitrin, cholesterol, etc.) keeping the sympathetic and parasympathetic nerve endings in a state of normal tone and maintaining a constant equilibrium. The organ itself, through the centripetal connections, acts to maintain the proper tonus of the vegetative sympathetic and parasympathetic centers. These centers again send centrifugal impulses via the sympathetic and parasympathetic tracts, which also act in maintaining tone in receptors. This forms the primary circle; a secondary one is associated. The glands of internal secretion, such as the suprarenal glands, which secrete amphotropic substances, have a dual vegetative innervation. We also know from Loewi's work that the organs give off amphotropic substances during functional activity. Grouped together, they may be called amphotropic secretory organs; in the charts they have been designated as "Amph." The impulses coming from the centers maintain a variable rate of activity in them, and this in turn regulates the peripheral factor.

B, sympathetic status, the sympathetic dot is heavier.

C, parasympathetic status, the parasympathetic dot is heavier.

D, amphotonic status, both dots are heavier.

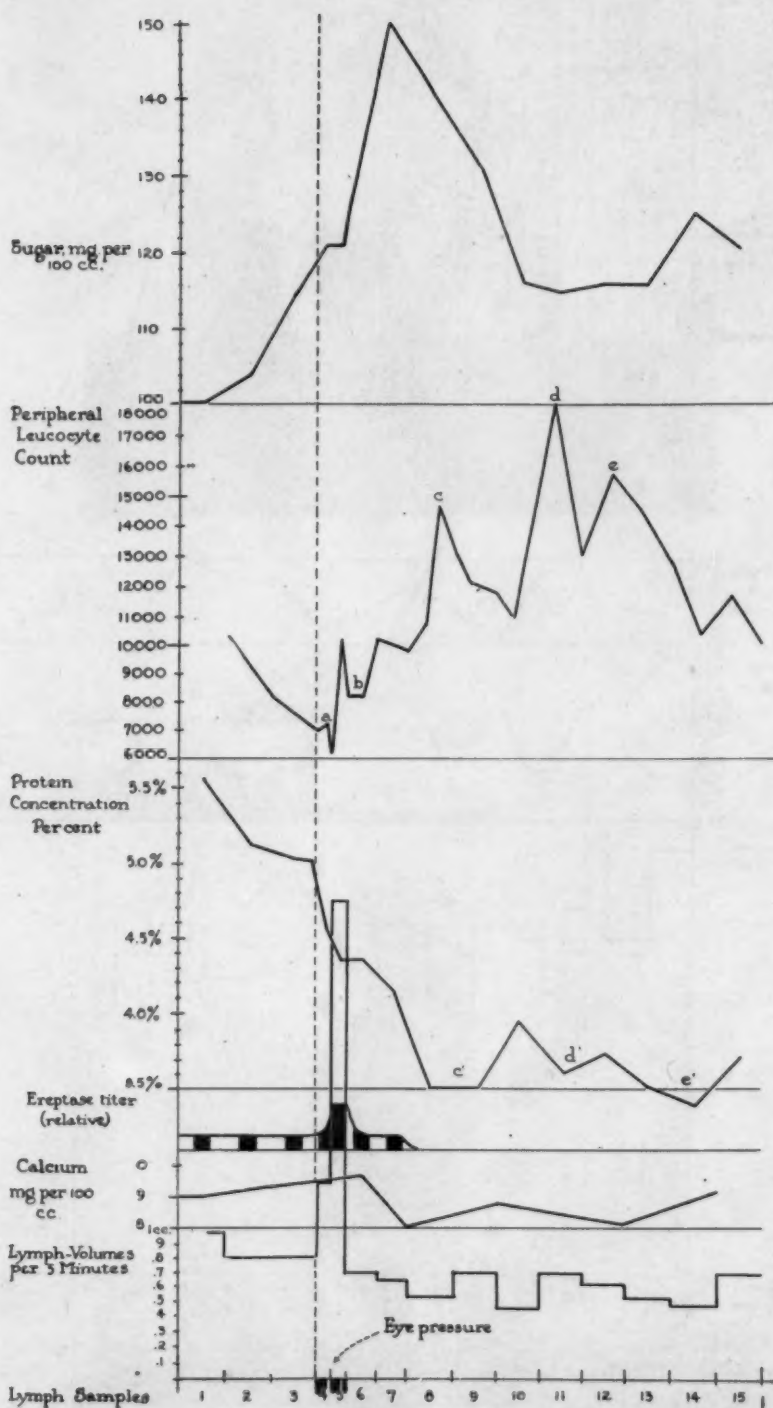


Chart 2 (exper. 18).—Rhythmic tonus waves (leucocyte curve) of increasing amplitude following bulbus pressure in dog.

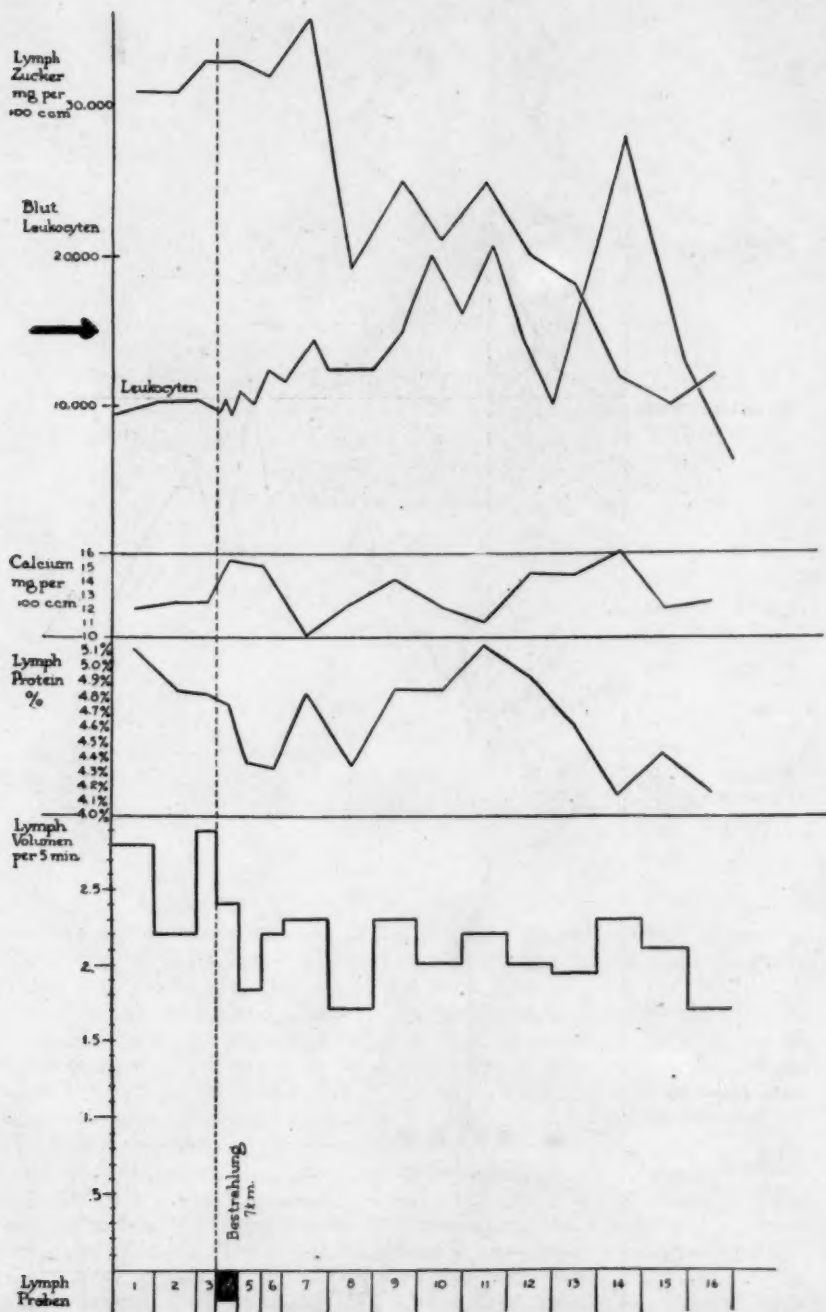


Chart 3 (exper. 2).—Rhythmic tonus waves of increasing amplitude following ultraviolet irradiation (from Petersen, W. F., and Von Oettingen, W. F.: Veränderungen der Lymphe beim Hunde nach Quarzlichtbestrahlungen, Arch. f. exper. Path. u. Pharmacol. **128**:160, 1927).

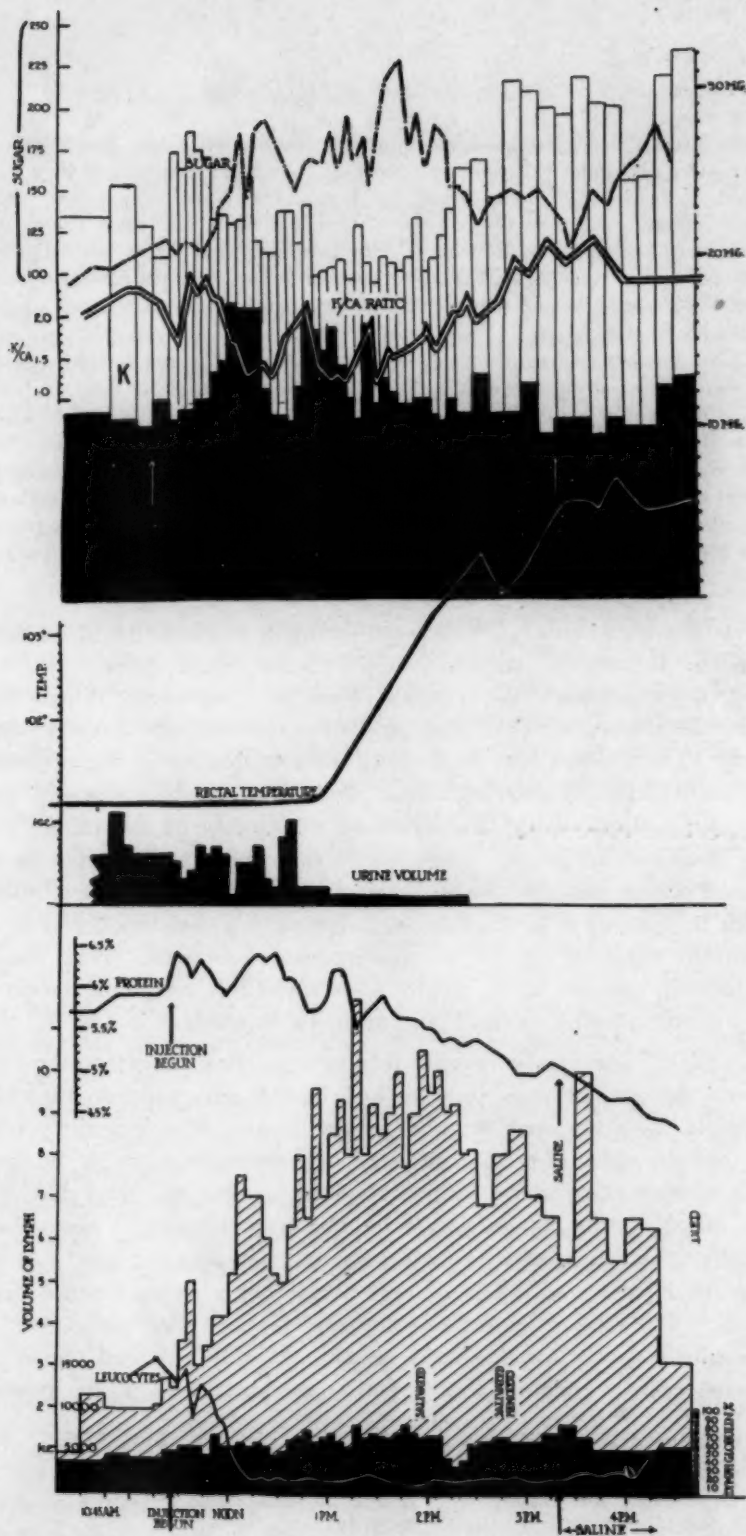


Chart 4 (exper. 18).—Typical fluctuations in the calcium and the potassium of the lymph with continuous injection of *Bacillus coli* (from Petersen, W. F.; Milles, G., and Müller, E. F.: *Ztschr. f. d. ges. exper. Med.* **60**:336, 1928).

minutes after the beginning of the injection, another after two hours and the fourth after two and a half hours. After that, the effects were effaced by a large amount of potassium coming from the injured red blood corpuscles. These chemical changes find their counterpart in the sugar curve, the lymph volume and the concentration of lymph protein. In this particular experiment, the leukocytes do not show a corresponding fluctuation, because the upset of the normal vascular splanchnoperipheral balance is so great that the peripheral region becomes fixed in a sympathetic status.

These fluctuations of alternating periods of stimulation and inhibition which find their expression in changes in the K/Ca ratio, in the sugar level, in lymph volume and in protein alterations, etc., form part of the splanchnoperipheral balance which Müller and one of us have discussed in various papers.¹⁵

In view of the foregoing observations, it is to be remembered that not only the general and local autonomic tonus is to be taken into consideration when the reaction of tissue is studied, but that one is dealing with a constantly fluctuating, labile condition and therefore the time element and the particular phase will always modify the response of the tissue.

Obviously, stimuli reaching a cell or organ when on the up or down grade, or at the peak, as contrasted with the trough, of a wave, may bring about diametrically opposite physiologic reactions. Tinel, Santenaise and Laurent¹⁶ have made analogous observations in anaphylactic shock. They found that such shock always accelerates the preceding condition (status); and that then a reversal sets in. "Vagotonic" persons, for instance, have first increased excitability of the vagus; then a reversal sets in during which no further shock can occur. In the "sympatheticotonic," on the other hand, vagotonia is secondary, during which the patient is in a condition receptive to a new shock and to the continued effect of any circulating antigenic substance. With such a mechanism, one can more readily understand this reciprocal action of the autonomic tonus on shock and of shock on tonus.

Schilf's View of Autonomic Antagonists.—Before leaving the more general aspects of this subject, we shall have to review briefly the views of Schilf.¹⁷ In line with the work of the Cannon school, Schilf pointed out that the older idea of a balanced nervous mechanism in the sense of a sympathetic-parasympathetic central antagonism, does not hold true for all tissues, there being a number in which only a sympathetic or only a parasympathetic innervation can be demonstrated. In the skin, for instance, we know of only sympathetic nerves for the sweat glands. Of greater importance for our problem, we know only of sympathetic nerves for the blood vessels. In only a limited region can parasympathetic (dilator) innervation be demonstrated, and the assump-

15. Müller, E. F., and Petersen, W. F.: *Klin. Wehnschr.* 5:53, 1926.

16. Tinel, J.; Santenaise, D., and Laurent, O.: *Bull. et mém. Soc. méd. d. hôp. de Paris* 47:471, 1923.

17. Schilf, E.: *Klin. Wehnschr.* 6:29, 1927.

tion that, because sympathetic fibers are vasoconstricting, vasodilatation must be accomplished by parasympathetic fibers, is at the least, not established, indeed is probably fallacious. Schilf frankly stated that this problem of nerve control of vascular dilatation is still an unsolved problem, an opinion which is apparently shared by Stöhr.^{17a} He emphasized that the organs predetermine their own course of action, and that we should stress organ reactions rather than attempt to force through a rigidly conceived idea of a vasomotor mechanism which actually is controverted by experimental facts. Particularly, the pharmacologic interpretation has done much to confuse the picture rather than to clarify it. The effect of a nerve impulse to an organ depends on the state of the organ to which that impulse is delivered. Schilf emphasized this, in particular, because "sick" organs react differently from normal organs.

Schilf's real contribution is his analysis of the fact that apparently antagonistic autonomic reactions (sphincterbladder mechanisms, for instance) can occur without nervous control and that such reactions are, from a broader point of view, not antagonistic but synergistic. So, too, for example, the control of temperature regulation, which, according to Cannon¹⁸ is largely sympathetic. Here, again we are dealing with an apparent balance of sympathetic and parasympathetic impulses; apparently antagonistic, actually synergistic.¹⁹

A number of Russian physiologists and clinicians have reached conclusions similar to ours, among them Platoff.²⁰

To this comes a more recent possibility that the sympathetic nerves are not only efferent, but also afferent, and may play a considerable rôle in periodic differences in the sensitivity to impulses;²¹ and the contention of Viale²² that the increase in the heart rate that follows cutting the vagi, is really due not to the deletion of inhibitory impulses, but to the increased secretion of epinephrine that follows. The correctness of such experiments must, of course, be first determined.

The discussion up to this point has, we believe, shown that we cannot arbitrarily select any one of the numerous factors that are involved in tissue activity and make it alone responsible for the clinical alterations that we see in every day practice. We are seldom justified in trying to establish purely endocrine imbalances; much less are we

17a. Stöhr, Philip, Jr.: *Mikroskopische Anatomie des vegetativen Nervensystems*, Berlin, Julius Springer, 1928.

18. Cannon, W. B.: *Tr. A. Am. Phys.* **44**:41, 1929.

19. Petersen, W. F., and Müller, E. F.: *The Splanchnoperipheral Balance During Chill and Fever*, *Arch. Int. Med.* **40**:575 (Nov.) 1927.

20. Platoff: *Russk. Klin.* **5**:3, 1926.

21. Förster: *Schless. Gesellsch. f. väterland. Kultur*, Breslau, *abst. Klin. Wchnschr.*, Feb. 1, 1929.

22. Viale, G.: *Boll. d. Soc. ital. di biol. sper.* **2**:54, 1927. Smirnow, A. J., and Schinoky, W. F.: *Ztschr. f. exper. Med.* **55**:24, 1927.

justified in trying to establish a purely nervous imbalance. We might do best by following Bergmann and speaking of certain groups of patients as "vegetatively stigmatized," and we should definitely discontinue regarding only the readily observable smooth muscle reactions as criteria of systemic autonomic change. The smooth muscle, with its tonus, represents primitive contraction; the twitch of the voluntary muscle appears much later. But this tonus requires little oxygen; it is a vegetative phenomenon regulated by the bio-electric (ionic) means. Later, we superimpose vegetative and voluntary nerves, as well as the specialized amines and vegetative poisons, epinephrine, histamine, choline, etc., which can obviously act, as Langley suggested, directly on the cell membranes by changing colloidal structure, not necessarily on the nerve endings.

And if, in clinical parlance, we continue to use the term "sympatheticotonic" or "vagotonic" in lieu of the broader one of "autonomic dysfunction" or "vegetative stigmatism," we should have clearly in mind the many reservations which we have indicated.

The entire field of the "autonomic nervous system" has been thoroughly reviewed by Kuntz;²³ or one may consult the older book of Müller.²⁴ The more clinical "Vagotonies, Sympathicotones and Neuritonies" by Guillaume²⁵ also offers much detailed information.

THE CHEMICAL EQUILIBRIUM

In the preceding discussion, we have traced the changes which have taken place from the original concept of functionally antagonistic sympathetic and vagus centers with resulting sympatheticotonia and vagotonia, to the present view with its emphasis on the autonomic status of the periphery. In the peripheral organ, we have already seen the presumptive influence of its milieu, its hormone content, its chemical equilibrium, etc., in determining local autonomic tonus and have also made note of the possibility of the effect of remote organs on such local tonus.

Rôle of Calcium and Potassium and the H-Ion Concentration.—The interest in the chemical phase goes back to the work of Jacques Loeb, who first emphasized the importance of the ions, particularly of calcium and potassium ions, in the control of cellular functions. The more recent and intensive cultivation of the field, particularly the application to clinical problems, comes from the school of Krause. Thus, Zondek,²⁶

23. Kuntz, Albert: *The Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1929.

24. Müller, L. R.: *Die Lebensnerven*, ed. 2, Berlin, Julius Springer, 1924.

25. Guillaume, A. C.: *Vagotonies, Sympathicotones and Neurotonies*, ed. 2, Paris, Masson & Cie, 1928.

26. Zondek, S. G.: *Klin. Wchnschr.* 2:382, 1923; 3:707, 1924; 4:905, 1925; *Die Electrolyte*, Berlin, Julius Springer, 1927.

after calling attention to the activity of ions on colloids in influencing their dispersion, hydration, etc., stresses the fact that two balances are of greatest physiologic importance, the H-ion concentration and the K/Ca ratio.

In general, we may accept the following:

With cellular activity, the calcium concentration of the cell membrane is diminished. Calcium leaves the cell, and there is a relative increase in potassium in the cell. The cell is more permeable, the protein becomes hydrated.²⁷

From this stage of activity, as one pole, the opposite extreme, of rest, is reached, with apparently a relative increase of calcium at the cell surface, relative impermeability, dehydration, etc. Calcium and potassium concentrations are therefore indicative of the swing of the pendulum of cellular activity (Osterhout; ²⁸ Lillie ²⁹).

These changes are cellular changes. They may be initiated by external impulses, a nerve impulse, for instance; the tone, however, will depend on a mechanism such as Danielopolu described. The concentration of either calcium or potassium in the serum may mirror the cellular change; but it must be clear that the serum levels do not necessarily change the reactions of the cells. The alteration of ionic concentration may ultimately bring about an abnormal vegetative reaction, but we may, and frequently do, find unipotential autonomic reactions without a corresponding consistent blood chemical picture.

The temptation is great to associate certain effects brought about by the increase of ionic concentration with definite autonomic nerve tonus; for instance, calcium with sympathetic effects, and potassium with vagus effects.

This association has been an outcome largely of clinical observations with injections of epinephrine hydrochloride. In the analysis which we present of our material on the basis of the epinephrine reaction, we have clearly shown that, while our outstanding "sympatheticotonic" persons had a lower K/Ca ratio (i. e., have relatively less potassium) than the outstanding "vagotonic" persons, there are many exceptions to the rule. But the fact that we find many exceptions to the rule, as did Brems,³⁰ and the fact that Jendrassik and Czike³¹ could find no constant correlation at all between the reaction to epinephrine and the K/Ca ratio do not for a moment vitiate the importance of the ion balance for these autonomic alterations. We must not forget that the epinephrine

27. Zondek, S. G.: *Biochem. Ztschr.* **132**:362, 1922.

28. Osterhout, W. J. V.: *Injury, Recovery and Death in Relation to Conductivity and Permeability*, Philadelphia, J. B. Lippincott Company, 1922.

29. Lillie, Ralph: *Protoplasmic Action and Nerve Actions*, Chicago, University of Chicago Press, 1923.

30. Brems, A.: *Acta. med. Scandinav.* **66**:207, 1927.

31. Jendrassik, L., and Czike, A.: *Klin. Wchnschr.* **6**:1521, 1927.

acts on the cell membrane—peripherally; the reaction of the cell depends on its status, tonus; i. e., on the ionic condition of its surface membrane. The relative ionic concentration of calcium and potassium in the adjacent cell fluids, quite apart from the blood, is only of secondary importance. Furthermore, all of our results and those of numerous others are estimated as total calcium and probably give a picture far different from the actual ionic calcium available.

Confusion of the Terminology Involved.—We must keep in mind, furthermore, that cell membranes are interposed between the cell protoplasm and the blood stream.

With a Donnan equilibrium here established, the amount of non-dialyzable ions combined with protein on both sides of the membrane and the total amount of protein becomes of greatest importance.³² We have shown by actual experiments (see chart 4) that with cell stimulation, calcium is liberated from the cell protoplasm and potassium there increased—corresponding to the time of vascular dilatation of the organ and therefore to a presumptive vagotonic status of the capillaries and tissues. This would mean that if we now use the term “vagotonia” as denoting a condition of tissue activity with capillary dilatation and increased permeability, then the blood stream should contain more calcium and relatively less potassium.

Actually, Kylin³³ found the “vagotonic” person, as clinically defined, to have more potassium and less calcium (higher K/Ca Ratio), and we, too, in using this clinical classification, can but confirm this.

Dresel³⁴ assumed that the blood of the “vagotonic” person is more alkaline and contrasts the resulting ionic states as follows:

<i>Vagotonic Status</i>	<i>Sympatheticotonic Status</i>
Tissues alkaline: little calcium-colloid, much potassium-colloid	Tissues acid: much calcium-colloid, little potassium-colloid
Blood alkaline: little ionized calcium, much bound calcium, little potassium	Blood acid: much ionized calcium, little bound calcium, much potassium

Accordingly, the “vagotonic” person should have a low K/Ca ratio, the physiologic effects being modified, however, by differences in ionization.

What we are actually facing here is merely a difference in definition. The clinical grouping of “vagotonic” does not define a person whose metabolism is increased and whose capillaries are permeable and dilated. This we should expect if in the vasomotor definition “dilatation” is synonymous with the “vagus effect.” On the contrary, the clinically

32. The capillary endothelium is permeable for proteins when stimulated.

33. Kylin, E.: Deutsche Arch. f. klin. Med. **149**:354, 1925; Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.

34. Dresel, K.: Klin. Wchnschr. **1**:1601, 1922; Klin. Wchnschr. **3**:311, 1924.

"vagotonic" person has a lower rate of metabolism and less permeable capillaries. Dresel was correct in theory, Kylin in practice. We can illustrate this further in the chemical changes of sleep.³⁵

Here we deal with a "vagotonia," even in decerebrate animals. There can be no doubt about the general condition of tissue rest; during this time, calcium diminishes in the blood and increases in the tissues and the potassium values show the reverse. The greater frequency of attacks of asthma and angina pectoris, the occurrence of pavor nocturnus, Pende ascribed to the vagus preponderance at night.

Clinical Grouping of Vagotonic and Sympatheticotonic Persons.—We have discussed this at some length to bring out the fallacy of our present classification of "sympatheticotonic" and "vagotonic." It should be given up, unless we are clearly cognizant of the various implications.

When we have spoken of the sympathetic status, we have always indicated the state of tissue rest: contracted vessels, calcium accumulation, dehydration.³⁶ When we have spoken of the parasympathetic status, we have indicated the state of the tissue with dilated capillaries, tissue activation, calcium dissimulation, hydration. When we have used the terms "sympatheticotonic" and "vagotonic," we have designated the clinical states as commonly interpreted.

And this brings up another apparent inconsistency. When smooth muscle contracts, the obvious inference is that the muscle tissue is active (it may contract, of course, with either sympathetic or parasympathetic stimulation), but actually during contraction the capillaries are also contracted, their endothelium is less permeable, metabolic processes are slowed, less energy is supplied. With relaxation comes dilatation of the vascular bed and increased permeability. Relaxation must, therefore, if we wish to be consistent, be the period of metabolic activity, i. e., the parasympathetic status in the sense that we have used it.

Now, it happens that when epinephrine is injected in small doses, the blood vessels dilate and the endothelium becomes more permeable. It is a true parasympathetic status of the tissues. With larger doses, the vascular musculature contracts, and the endothelium becomes less permeable. These are direct cellular effects and take place presumably without nervous mediation. This is a true sympathetic effect. But the many other effects initiated at the same time by the large dose of epinephrine result in a most complex picture.

35. Fischer, H.: *Biochem. Ztschr.* **193**:169, 1928.

36. If the sympathetic status with contracted vessels occurs for a long period of time with a resulting stasis in the capillaries, it is possible that the cellular metabolism of the region will show a condition far different from "rest," i. e., rather an asphyxial stimulation. Such states may presumably occur in the peripheral tissues during a chill.

Of course, Zondek³⁷ was careful to state that the vagus effect is like the potassium effect; he never insisted that the two are identical, although, in general, it is assumed that the nerve impulse makes use of the ions in upsetting the membrane equilibrium. With this consideration, one can understand why in certain clinical conditions—urticaria, for example—the calcium level may be normal and yet the administration of calcium be, at times, useful, at other times, without effect. We can understand why the level may be constant—and it is one of the most firmly held of the balances, as Kroetz³⁸ has shown, with a negative balance; i. e., cells may be losing calcium, but the level remains the same, as Aub³⁹ and his associates have so clearly demonstrated in exophthalmic goiter. And we can understand why the level may be low in the blood, while the relation in the cell membranes is at its proper level.

Rôle of Cholesterol.—There seems to be some basis for the belief that cholesterol is involved as an intermediary in the ionic autonomic mechanism that we have been discussing,⁴⁰ and here again we are dealing with a confusion resulting from the presumable effects of cholesterol as a component of the cell membrane and cholesterol free in the blood stream. It is, of course, possible that an increase in the cell membrane can be present at the same time that we have an increase in the blood stream. The possibility also exists that with an active exchange going on between the two, high membrane content may be associated with low plasma content and vice versa. Just as with the ionic balance, the membrane relations present great complexity, with innumerable physical and chemical differences, free and saponifiable forms and the ability of the blood proteins to form protective colloids all influencing the ultimate balance. Mjassnikow⁴¹ definitely associated the increase in blood cholesterol with hyperasthenia, not only in the apparently normal condition, but in the associated diseases, of this constitutional type, i. e., gout, obesity, hypertonia, asthma, hay fever, gallstones, etc. This cholesterol increase appears to be true for our "heavy" group, as well.

But Dresel and Sternheimer⁴² definitely placed cholesterol in the sympatheticotonic group, counterbalanced by lecithin as a parasym-

37. Zondek, S. G.: *Klin. Wchnschr.* **6**:1951, 1927; footnote 26, second reference.

38. Kroetz, C.: *Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong.* **40**:91, 1928.

39. Aub, J. C.; Bauer, W.; Heath, C., and Roper, M.: *J. Clin. Investigation* **11**:97, 1929.

40. Westphal, K.: *Ztschr. f. klin. Med.* **101**:545, 566, 584 and 603, 1925.

41. Mjassnikow, A. L.: *Ztschr. f. klin. Med.* **105**:228, 1927.

42. Dresel, K., and Sternheimer, R.: *Klin. Wchnschr.* **4**:816, 1925.

pathetic agent. Glaser⁴³ discussed some of the relations in arteriosclerosis and found, as had Wacker and Hueck,⁴⁴ that the injection of epinephrine hydrochloride increases the amount of cholesterol in the serum. A complete discussion of the literature would be superfluous at this time. We merely mention the probable rôle of these lipoids in the chemical and physical equilibrium that is involved in the autonomic background.

THE SKIN

Its Autonomic Importance.—Among the vegetative organs concerned with our immediate relation and adjustment to the outside world, none is of greater importance than the skin; it is unfortunate that it has been largely ignored by the physiologist, perhaps, because in his preoccupation with the experimental animal, he has failed to realize how far different the human skin is in its reactivity from that of any of the lower animals; perhaps because he has regarded the skin merely as a protective mechanism—the “overcoat” with which Engman has chided the dermatologists for their narrow point of view.

As a matter of fact, the skin is the reactive membrane for the whole organism, just as the cell membrane is for the individual cell, and with almost as many important and sensitive receptors and reactive possibilities. Clinical observation has always recognized the interrelation of the skin and the deeper tissues. The so-called antagonism of visceral and skin tuberculosis and syphilis is one example. So, too, is the protective immunity established by the exanthems; and the tradition that a good reaction of the skin protects against internal complications in the same group of infections is established folklore. More recently, the rôle of the skin in allergy and the therapeutic possibilities incidental to stimulation of the skin have raised the clinical interest and aroused considerable investigative curiosity. Müller and Delbanco⁴⁵ developed the idea of the skin as a vegetative sense organ and in line with von Groer⁴⁶ emphasized the skin as a mediator of autonomic regulations by virtue of both its chemical and its physical potentialities.

As is well known, the latitude of the adaptability of the skin to an insult or to a change in environment is great, must of necessity be great, because on it depends the life of the whole organism.

We should therefore like to develop the subject of the importance of the skin and its autonomic tonus in more detail and shall use bacterial invasion as an example of the effect of an abnormal external insult.

Local Resistance.—The sum total of the processes involved may vary from the normal physiologic responses, or what may be termed

43. Glaser, F.: *Klin. Wchnschr.* 6:2377, 1927.

44. Wacker, L., and Hueck, W.: *München. med. Wchnschr.* 60:2097, 1913.

45. Müller, E. F., and Delbanco, E.: *Dermat. Wchnschr.* 87:1348, 1928.

46. Von Groer, F.: *Klin. Wchnschr.* 6:96, 1927.

"local tissue resistance," all the way to the severe inflammatory reactions elicited when certain organisms or biologically active toxic substances penetrate the superficial layers. The human skin, as we have pointed out, is much more reactive both specifically and nonspecifically than the skin of other animals.

The inflammatory reaction differs in degree from the normal physiologic response, the direction of the change is apparently uniform at the onset in both cases. Both the "local resistance" of the normal and undamaged tissue and the inflammatory resistance depend to a marked degree on the preexisting vegetative status of the tissues.

In order to maintain local resistance of the tissue an unaltered function of the cellular elements is the prime requisite; the second is an undisturbed replacement of the energy requirements during the course of normal metabolic processes. This involves a definite orientation of the autonomic apparatus of the involved tissue, so that the full development of tissue function and energy supply can be maintained.

Certain cells, particularly those that are to some extent free from cell complexes and organs (reticulo-endothelium and the resting wandering cells of Maximow), are more independent in their adaptability to changes in the environment insofar as they seem less subject to the influences which are operative when cell groups are involved.

On the other hand, in the organized tissues, every reaction of one organ involves more or less directly certain fundamental correlations with all the other organs and tissues. Brown's⁹ work makes this interrelation evident. Remote organs, under conditions of stimulation, may then act either as accelerators or inhibitors of the function of other organs, whereby the adaptability of a remote zone may be enhanced or retarded.

The law of Dastre and Morat and our own experiments with the splanchnoperipheral balance of the organs show this clearly. If, for any reason, we observe a sudden increase of activity of the abdominal organs with increased vascularity of the region, there is not only a diminished amount of blood in the peripheral vascular bed, but also a diminution in the functional capacity of the peripheral organs associated with synchronous contraction of the vessels.⁴⁷

We have already touched on the autonomic vascular mechanism involved, in connection with the paper of Schilf. We shall here limit ourselves to the question how far such alterations (which are constantly occurring under physiologic conditions) influence the organs and tissues

47. Fremont-Smith, F.; Morrison, L. R., and Makepiece, A.: *Proc. Am. Soc. Clin. Investigation*, May 6, 1929; abstr., *J. Clin. Investigation* 7:489, 1929. Smith, Morrison and Makepiece have recently made observations on the capillaries during chill and find a complete stasis in all visible capillaries due to the constriction of the terminal arterioles.

with a possible loss of the local resistance of the tissue and predisposition to disease.

Herpes and Splanchnoperipheral Balance.—On the skin, in the nasal mucous membrane, and in the gastro-intestinal mucous membrane, pathogenic organisms live without further penetration, that is, until at some time a slight trauma, a "cold" or some other indisposition leads to local infection. With mechanical injury and its obvious disturbance, the lowering of the resistance of the tissue is easily understood. It is much more difficult to understand the other types of susceptibility, the appearance of a labial herpes for instance, with a sudden onset of fever. We know its pathognomonic interest and the enormous spread occasionally seen in association with the chill of an infection with *Bacillus coli*; we also know the nasoparasitic character of herpes virus.

The ubiquitous virus previously present in the adjacent surface of the skin suddenly penetrates the superficial layers and, from the clinical point of view, becomes virulent at the time of systemic reaction incidental to the generalized disease. The virus, having once penetrated, meets with further resistance in the form of local inflammation, the intensity of which is usually sufficient to check the further spread.

This picture is a typical example of the transition of a previously latent organism to full virulence as the result of the failure of local resistance of tissue. The question as to the cause of such failure with the onset of the chill and high temperature is of far greater interest than that involved in the mechanism of the infection of the pelvis or uterus with *B. coli* in septic abortion. Other herpetiform invasions are apparently related to similar processes: the herpes infection of the skin in certain periods of the menstrual cycle, and in certain persons during acute indigestion, etc.

The cause is always the same. A sudden and intense increase of activity in the splanchnic region involving marked increase in the vascular bed and increase of the secretory function reflexly involves a change in the peripheral tissues. The change includes a diminution in the size of the vascular bed and a reduction of cellular activity. The periphery becomes less capable of reaction to external stimuli for the reason that reactions which under normal conditions are associated with increased vascularity and increased metabolic cell processes are either diminished or do not make their appearance.

A second possibility must be considered. The stasis of the peripheral capillaries may be of sufficient duration to bring about injury of the more superficial epithelial cells—cells that normally are undergoing necrobiosis. This dysfunction incident to the stasis may be sufficient to account for the penetration.

Such alteration of the distribution of the blood takes place in all conditions associated with fever. A similar redistribution in the vascular

bed together with an increase of the secretory function of the stomach and other large glands of the abdominal region occurs in varying intensity during the menstrual cycle, during migraine and even during digestion, more evident in certain persons, when we see it as part of the "Widal hemoclastic crisis."

The cause of this abdominal splanchnic dilatation may vary in individual cases, but the reaction of the organs and the vessels in the splanchnic region is fundamentally the same. It is unidirectional, and it is associated with peripheral constriction made apparent in the pallor of the skin, with headache, with nausea, etc. In the chill of an infection with *B. coli*, one can observe the most intense form of this splanchno-peripheral change. The enormous increase in activity of the liver which results from the systemic invasions is associated with a decreased flow of blood at the periphery and a diminution of all peripheral cellular function. It is this latter change which is of the greatest practical importance.

Heat radiation and sweat formation are clinically familiar to us. Their inhibition, even if transient, is part of the mechanism that causes fever, because the dissipation of heat produced by the increased activity of the splanchnic organs is thereby checked. Only when, with gradually diminishing activity of the liver, the correlated inhibition of the autonomic functions of the skin is lessened, does the temperature begin to fall. During the menstrual cycle, similar conditions may prevail even though the clinical symptoms are less apparent. Here, too, one finds minor fluctuations of temperature that have the same physiologic basis, though here without infection.

Local tissue resistance, which is most impressive in the skin, is subject to the same inhibitory influences. Reactions of the skin associated with increased resistance to infection are hard to recognize. It is true that our clinical experience indicates that a skin or a mucous membrane with good circulation is less apt to become infected, and that healing takes place more rapidly under such conditions. This might be apparent, too, from the relative freedom of the exophthalmic patient from infections of the skin.

Inhibitory influences on the skin, with diminution of its autonomic adaptability, also become apparent only when every day demands are not met in the normal fashion, for example, when one has a virus present and finds that with lowering of the local tissue resistance, the virus is enabled to penetrate into the deeper tissues.

It is of secondary importance whether such an inhibition takes place primarily through nerve impulses, through alteration of the metabolism or through endocrine alterations which secondarily lower the resistance toward the infections.

We ⁴⁸ have previously noted definite autonomic influences on the skin of women during the menstrual cycle. In the absence of a potential virus on the skin, these alterations are clinically innocuous because, practically, one is dealing only with a susceptibility toward infection. Only when one is dealing with a potential infection, as in persons harboring the herpes virus, does the periodic depression of resistance become apparent.

Respiratory Tract.—In the nasopharynx, similar autonomic influences become apparent. In chill and in high fever, the mucous membranes of the mouth and the nose are dry because the cell functions of the mucous membranes are definitely depressed or inhibited. The coated tongue is a manifestation of the same influences.

Glands and mucous membranes are in themselves uninjured; it is only their functions which are diminished during the time of fever. Despite urgent need and mechanical stimulation through chewing and sucking and contact with food, the formation of saliva is inhibited because of the vegetative contraction of blood vessels, as well as the vegetative inhibition of the cell functions. The same condition holds true for the hunger sense. The diminution of contractions that we ⁴⁹ have demonstrated for the stomach during this time is part of the picture of diminished appetite (the opposite vegetative orientations of salivary glands, mucous membranes and tongue, on the one hand, and of stomach, liver, etc., on the other, are particularly marked in these cases, as we have shown previously). The stomach during this time is under a condition of stimulation which leads to a considerable secretion of a strongly acid stomach juice.

Other infections of the mucous membranes besides herpes are well known during fever, for instance, the inflammatory reaction of the upper part of the respiratory tract, as well as of the conjunctiva. Such inflammatory reactions are by no means to be regarded as part of the primary infection, but are merely manifestations that these tissues for the time being have lost their resistance either partially or entirely, resistance which under normal conditions would be more than able to cope with every day irritations. Here, for instance, could be mentioned the conjunctivitis occasionally seen with the flare-up of a localized pulmonary tuberculosis, so characteristic that it may be regarded as a distinct symptom of activation.

We shall show later on that the exanthems of the acute exanthematous infections (scarlet fever, measles) only become possible because

48. Petersen, W. F., and Milles, George: Relation of Menstruation to Permeability of Skin Capillaries and the Autonomic Tonus of Skin Vessels, *Arch. Int. Med.* **38**:730 (Dec.) 1926.

49. Müller, E. F., and Petersen, W. F.: *München. med. Wchnschr.* **74**:531, 1927.

the skin and the mucous membranes have a diminished resistance toward the circulating toxin. Müller, Metz and Myers⁵⁰ demonstrated such a pathogenicity for one exanthematous disease due to a known toxin, namely; the arsenical dermatitis following arsphenamine.

Even the occurrence of halitosis in severe infections is due to the lessening of cell activity in the mucous membrane of the mouth, with diminution of the bactericidal power. The idea that the fetor is of stomachic origin is incorrect, for the growth of bacteria in the stomach is not increased during fever, though the bacterial flora may ascend to the higher levels of the gastro-intestinal tract, as has been demonstrated by Arnold and Brody.⁵¹ As a matter of fact, the stomach contents, when removed, have no such fetid odor. Soor paradentosis, caries and the pityriasis versicolor of the cachectic patient have a similar origin insofar as the loss of the resistance of the tissue makes possible the infections named. The loss of hair and the impairment of the growth of the nails give further evidence of the peripheral vascular disturbances.

Before we enter into a discussion of similar changes in the other organs, we must discuss for a moment those reactions which serve for the protection of tissue when toxic substances or a virus have entered the skin and the mucous membrane. We characterize them as inflammatory. Intensity of change, and this in relation to the protection of tissue means the effectiveness of change, also depends on vegetative orientation of the tissue as such. Examples of such influences are well known. With the onset of fever—let us say the sudden onset of an angina—the exudate of a gonorrheal infection ceases for a time. The formation of pus in a sterile turpentine abscess during a fever starts after defervescence; all evidences that an autonomic influence is of paramount importance in local inflammatory processes.

The work of Kauffmann⁵² and of Petersen⁵³ presents further examples. Particularly, the work of Kauffmann with cantharides blister during the course of lobar pneumonia seems to us of particular significance, because Kauffmann carried out his experiments without considering the autonomic orientation in its influence on the metabolism and reactivity of the tissues. During the course of the febrile stage of pneumonia, he observed a decided impairment of reaction. He said:

The exudates are peculiarly poor in the cellular elements. Among the cells present lympho-histiocytic elements are completely absent, as are also eosinophile cells, so that the exudate consists practically of neutrophile leukocytes. But even

50. Müller, E. F.; Metz, G. P., and Myers, C. N.: Arsenic Lesions of the Skin, *Arch. Dermat. & Syph.* **15**:186 (Feb.) 1927.

51. Arnold, L., and Brody, L.: *Am. J. Hyg.* **6**:672, 1926.

52. Kauffmann, F.: *Krankheitsforschung* **2**:372, 1926.

53. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch. Int. Med.* **38**:663 (Nov.) 1926.

the immigrative cell elements so represented are increasingly diminished in the more severe disease processes. It is only with the crisis—when the inhibitory influences on the skin have disappeared, that inflammatory irritability and particularly the intensity of the cellular processes again increase.

In this work with the cantharides blister, Kauffmann therefore described the dependence of the inflammatory reaction on the vegetative orientation. Some years ago, Müller⁵⁴ pointed out that every collection of leukocytes was associated with a dilatation of vessels. Such dilatation is inhibited during a period of general reaction to infection. Herein, just as in the inhibition or diminution of the mobilization of tissue cells in the inflammatory exudate, we can recognize the negation of this phase of tissue protection of the skin at times when the center of metabolic activity of the body has been transposed to the internal organs.

Gastro-Intestinal Tract and Change of Temperature.—The reversal of such vegetative orientation can also be established. Arnold¹ showed that when the blood vessels of the skin and the peripheral tissues are active, the bactericidal properties (that is the self-protection of the tissues) in the gastro-intestinal tract, particularly of the duodenum and the upper jejunum, are diminished. Man, as well as animals, exposed to heat and high humidity show, not only a coincident diminution in the secretion of the gastro-intestinal fluids, but a diminution in the normal response of the gastro-intestinal tract to food. If one examines dogs in superheated rooms, bacteria are found passing the stomach and duodenum practically in 100 per cent of the cases, whereas in the animals kept under normal conditions of temperature the bacteria are killed. If one feeds such overheated animals meat poisoned with enteritis toxin, the animals die, whereas animals kept at normal temperature or a cool temperature survive. If one measures the organic function of these animals in terms of stomach and bile secretion, following ingestion of poisoned meat, then one observes a marked and occasionally a total inhibition in the animals kept too warm and an enormous reaction in the control animals. In the human being, we also have observed this diminution with external heat as contrasted with normal temperature and a correspondingly increased reaction at the time of actual chill. The susceptibility to gastro-intestinal infection increases notably at times of increased external temperature. This is not only the case when infected food or pathogenic organisms pass in fully virulent form through the stomach to the gastro-intestinal tract. Even the normal gastro-intestinal parasitic flora is no longer indifferent under these conditions. Thus, Arnold⁵⁵ showed that with increasing

54. Müller, E. F.: München. med. Wchnschr. 69:1506, 1922.

55. Arnold, L.: Am. J. Hyg. 8:604, 1928.

external temperature the flora changes its character, as well as its range. Characteristically, the lower gastro-intestinal flora invades the upper region of the gastro-intestinal tract. Similar conditions underly the manifestations of gastro-intestinal morbidity in populations at the beginning of the warmer periods of the year or in persons who go from cold to tropical climates. With the associated increased activity of the periphery of the body, the functional capacity of the abdominal organs is diminished.

This, too, is not necessarily dependent on the actual height of the external temperature, but rather on the reactivity of the skin and the lungs at the time, and on the autonomic impulses that under those conditions leave the periphery and influence the gastro-intestinal tract and the abdominal group of organs, in general. The decrease of resistance of the gastro-intestinal wall—in other words, the increase of susceptibility—in warm climates and in the hot summer is therefore most apparent in the unacclimated persons, that is, with sudden and unaccustomed changes, rather than in persons who gradually accustom themselves to higher temperatures. This point is of epidemiologic importance for a variety of gastro-intestinal infections, as well as for tropical diseases.

In the liver, too, the local immunity of the parenchyma is clearly dependent on the autonomic orientation of the tissues and is only effective when inhibitory impulses are not predominant.

The normal increase in activity of the liver in chill and fever has been previously described in some detail.⁵⁶ Secretion of lymph and bile increases tremendously and with it vascularization, function and cell permeability. The marked increase of the permeability of the cells and tissues, in general, does not involve a necessary penetrability for all substances present in the blood. Despite continuous intravenous injection of living *B. coli* in the animal over experimental periods lasting for hours, the lymph of the thoracic duct remains free from bacteria. That is, the sterility of the lymph is constant as the function of the liver increases. On the other hand, bacteria are being constantly excreted into the bile passages. If such an experimental injection of *B. coli* is continued long enough (for ten, fifteen or twenty hours), one arrives at a time when the function of the liver is apparently rapidly diminished. At this time, the peripheral constriction of the vascular bed is also broken, and the animals show a peripheral hyperemia. In the liver, the vessels contract, the permeability of cell and tissue is diminished, as is the production of lymph and bile. At the time of this injury, red blood corpuscles appear in the lymph stream, proteolytic

56. Petersen, W. F.; Müller, E. F., and Boikan, W.: *J. Infect. Dis.* **41**:405, 1927.

enzymes are markedly increased, the temperature falls, and some of the bacteria make their way into the lymph stream. Later this picture may be reversed.

Here, too, we see that the characteristic balance between the skin and the mucous membranes of the mouth, on the one hand, and the mucous membranes of the gastro-intestinal tract, on the other, may also influence the local resistance of tissue in other organs by means of a supererogated vegetative control.

These observations seem of certain importance in various directions, not only for the understanding of such processes as herpes, the infections of the mucous membranes of the mouth with parasitic invaders previously latent, and the catarrhal conditions of mucous membranes, in general, during infectious diseases and following chilling of the body surfaces, but for the understanding of gastro-intestinal manifestations in persons in unaccustomed warm climates, and of the status of the liver in the course of septic infections. From them we may be permitted to make certain deductions concerning the susceptibility of organs and tissues, in general.

The protection of normal tissues against an infection does not depend to any great degree on immune powers of the serum, but is, as every other function of the body, due to the cellular activity of the tissues and therefore is closely associated with the vegetative impulses and the vegetative status as particularly manifest in vascular alteration. One realizes, too, that the cellular tissue functions, on which local resistance depends, are controlled (as are all other functions of cells and tissues) in their responses and activity not only by the anatomic and functional activity of the individual elements as single cell organisms might be, but by certain limitations of their potential possibilities placed on them by more remote organic processes that directly influence the intensity of the vegetative orientation not only of the entire body, but of the local organs and tissues. It is possible, therefore, that with complete anatomic and physiologic integrity of the tissues, and despite the manifest danger due to the local infection, the local resistance of tissue may fail because it is inhibited through influences which, originating in remote regions, influence the local functional status. How this inhibition of functional response in the tissues may be brought about is clinically and practically unessential. At least two possibilities exist. Primarily, the diminution of function may be secondary to vascular dysfunction with an associated diminution of energy resources. Secondly, it may be directly imposed by the vegetative nervous impulses, or by chemical or hormone alterations acting on the blood vessels, as well as on the individual cells, either immediately or mediately.

The only fact that is of practical importance is that the local protection of the tissues, particularly those that have come in contact with

the surrounding world, is associated with and dependent on a superimposed vegetative orientation. Important is the knowledge that influences which may change the vitality of tissues, the functional capacity of the tissue and therefore the self-protective mechanism may remain objectively unnoticed, since they can be measured only in the end-result. In terms of relative resistance, they are perceptible only indirectly, that is, when functional inhibition has gone so far that the infection actually takes place.

It is not the mechanical integrity of the skin that offers the most effective protection, it is the vegetative condition of the tissue during which the adaptability of the cells can be developed to its maximum potential degree. It is seen that, on the basis of the splanchnoperipheral balance in the community of organ response, the more intense activity of the one group is balanced by a relative inhibition of the vital activity and capacity of another group, and that local resistance, as a measure of metabolic activity, as other functions, loses some of its potentiality under the influence of inhibitory forces. The local resistance of tissue is intimately bound up and dependent on local tissue elements and their functional capacity. With lowering of this functional capacity of the tissue, there occurs a lowering of the resistance of the tissue, irrespective of the origin of these inhibitory influences from without or from within, or of whether they are initiated by tangible organic changes or by psychic processes. The head cold, for instance, is not the result of a change of temperature to which one may have been exposed, but is the result of an individual difference in local resistance. Even in a severe draft with a considerable cooling, the temperature of the mouth, of the nasopharynx, of the musculature and of the joint cavities may remain approximately the same. With long continued intensive cold of the skin, of course, all the tissues and organs respond, the peripheral ones with a relative diminution of vascularity. We are therefore of the opinion (because of clinical observation) not only that articular rheumatism may be due to certain types of organisms, but that the joint membranes and the musculature have definite fluctuations of resistance against these invaders depending on the vegetative orientation of the moment. The Weber phenomenon is based on the fact that sudden displeasure or sadness leads to a diminution in the amount of blood in the periphery with a corresponding increase in the abdomen. But in psychic trauma, such as fright or fear or worry, a severe and long continued physical influence on the body can be brought about. In all of these one finds pallor of the skin, dryness of the mouth, loss of appetite, etc. One can readily see that the influences that make manifest many organic disturbances in association with psychic trauma do so because of the fundamental and underlying autonomic changes that we

have discussed in relation to the herpes virus. The organic changes depend, as this does, on the vegetative ability and adaptability of the local tissue.

EXOPHTHALMIC GOITER

Recently, Warthin,⁵⁷ in a discussion of exophthalmic goiter, reaffirmed his conviction that the underlying factor is constitutional, symptoms developing only as a result of abnormal reactions to stimuli which in a normal person would be met by physiologic adaptation. Oswald,⁵⁸ too, believed that the effect on the thyroid gland depends wholly on an instability of the nervous system in certain persons, an instability that Kessel, Lieb and Hyman⁵⁹ place in the myoneural junction. Warthin, furthermore, believed that "Graves' constitution" is associated with a "thymic-lymphatic" status and is characterized by hyperplastic primitive lymph nodes in the gland itself, which is involved in the disease only incidentally. Aschoff and Krehl both expressed similar views, and Miller⁶⁰ emphasized the probability of at least two active factors in the disease, one not identical with the substance that increases the basal metabolism.

There is a growing volume of clinical comment in agreement with this view.⁶¹ Bram⁶² tersely differentiated toxic adenoma by stating that here "the thyroid makes the body sick; in exophthalmic goiter (a constitutional disease) it is the body that makes the thyroid sick."

Our previous,⁶³ as well as present, series have made apparent a striking increase in capillary permeability in exophthalmic goiter, which, we believe, is basically associated with the clinical manifestations. Such an increase in permeability has been suspected as a result of the previous work of Eppinger and Hess. Gellhorn⁶⁴ has more recently proved the increase in permeability by direct experiments. Weil⁶⁵ drew the conclusion that the increase in permeability is to be correlated with, first, the increase in absorption and, second, the increased electrical conductivity of the tissues, and finally, with the increase in cell division

57. Warthin, A. S.: *Ann. Int. Med.* **2**:553, 1928.

58. Oswald, A.: *Klin. Wchnschr.* **4**:1053, 1925.

59. Kessel, L.; Lieb, E. C., and Hyman, H. T.: *A Study of Exophthalmic Goiter and the Involuntary Nervous System*, *J. A. M. A.* **79**:1213 (Oct. 7) 1927.

60. Miller, J. L.: *Proc. Inst. Med. Chicago* **7**:89, 1929.

61. Zondek, H., and Bansi, H. W.: *Klin. Wchnschr.* **8**:1697, 1929.

62. Bram, I.: *M. J. & Rec.* **129**:579, 1929.

63. Petersen, W. F.: *The Permeability of Skin Capillaries in Various Clinical Conditions*, *Arch. Int. Med.* **39**:19 (Jan.) 1927.

64. Gellhorn, E.: *Das Permeabilitäts Problem*, Berlin, Julius Springer, 1929, p. 341.

65. Weil, R.: *Klin. Wchnschr.* **8**:852, 1929.

observed in exophthalmic goiter. Weil found that thyroxin in small doses increases liver autolysis, which is due, presumably, to colloid chemical membrane changes with increased permeability. The clinical interest, as well as the physiologic interest, must therefore turn from the supposition that the effect is on the nerve endings as an intermediary. We are really dealing with a direct membrane change.

Dresel,⁶⁶ who also observed an increase in amino acids in liver autolysis following the injection of thyroxin, made use of the increased oxidation in the liver and testicle by injecting small doses of blood of the exophthalmic patient into a mouse.

The liver under these conditions becomes glycogen-free. From his experiments he concluded that the active agent circulating in the blood of the exophthalmic patient is far more active than any thyroxin preparation.

Mora⁶⁷ studied the shortening of the resorption time of intracutaneously injected salt solution in exophthalmic goiter, and Asher⁶⁸ made use of a similar dye test to demonstrate the central (sympathetic) effect on the thyroid gland.

The increase in permeability associated with increased metabolic activity should be followed by a negative calcium balance—and that it is, was recently demonstrated by Aub⁶⁹ and his associates, who also noted that osteoporosis may appear during the course of the disease.

Our observations indicate that the increased permeability determined by the blister is not necessarily related to the increased basal metabolic rate. In this respect, the results correspond with those noted in the markedly sympathetotonic and nervous group in the members of which we observed an increased permeability without an increase in the basal rate. This fact, among others, inclines us to the view that we are dealing with two distinct factors—one, an underlying change in tissue reactivity, and another which is distinctly related to the calorogenic effect of the thyroid secretion. The question concerning the duality or multiplicity of the effect on the thyroid gland has repeatedly been raised; most recently by Csépai,⁷⁰ who, judging only by the effects on blood pressure, denies the probability.

The reactivity of the skin in patients with exophthalmic goiter presents a number of interesting features. The erythema after the applica-

66. Dresel, K.: *Verhandl. f. inn. Med. u. Kinderh.*, Berlin, Jan. 7, 1929; abstr., *Klin. Wchnschr.* **8**:425, 1929.

67. Mora, J. M.: *J. M. Sc.* **177**:153, 1929.

68. Asher, L., and Pfluger, O.: *Ztschr. f. Biol.* **87**:115, 1927.

69. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: *J. Clin. Investigation* **7**:97, 1929.

70. Csépai, K., and Fernbach, J.: *Arch. f. exper. Path. u. Pharmakol.* **129**:256, 1928.

tion of ice appears rapidly, and the resistance of the skin to electric current is lowered, as Richter ⁷¹ has previously noted.

Lueg and Grassheim ⁷² studied the capacity of the skin for polarization in thyroid disease and noted that the increase in the basal metabolic rate usually parallels the increase in capacity for polarization. Curiously enough, the upper and lower portions of the body may show considerable difference. Nothhaas, ⁷³ in examining the dermatographic reaction, found a longer latent period in exophthalmic goiter.

Hoke ⁷⁴ made use of a traumatic reaction (carbolic-salt) and demonstrated an increased reaction of the skin in exophthalmic goiter and also after injections of thyroxin. Similar increases in reactivity were noted when milk or typhoid vaccine was injected.

In our preliminary discussion, we pointed out the occurrence of a dissociation of certain changes of the skin from the metabolic rate. We called attention to the fact that, following operation, the basal metabolic rate might return to normal but certain of the alterations of the skin become more pronounced. Such a dissociation of symptoms is, of course, a common observation in exophthalmic goiter and merely confirms our impression that the underlying change is dual. The treatment, too, would indicate this. Zondek ⁷⁵ grouped the methods under three heads: (1) operative removal of the thyroid gland, (2) fixation of thyroxin in the thyroid gland (with iodine) and (3) treatment with certain of the narcotic drugs that change the surface of the cell.

König ⁷⁶ added to this, thorough alkalization, a procedure that might seem logical from the probable effect on the membrane of the cell.

THE NERVOUS PATIENT

It will be recalled that our nervous patients had a relatively low level of potassium with a practically normal level of calcium in the serum, were, in general, thin, usually showed an increased permeability of the capillaries, had a high resistance of the skin to electric current and a rather delayed reaction to ice.

Glaser ⁷⁷ reported that there were observable differences in the amount of calcium in the serum in different psychic states in the same person.

71. Richter, C. P.: Electrical Skin Resistance: Diurnal and Daily Variations in Psychopathic and Normal Persons, *Arch. Neurol. & Psychiat* **19**:488 (March) 1929.

72. Lueg, W., and Grassheim, K.: *Ztschr. f. klin. Med.* **110**:531, 1929; *Klin. Wchnschr.* **7**:647, 1928.

73. Nothhaas, R.: *Klin. Wchnschr.* **8**:820, 1929.

74. Hoke, E.: *Wien. klin. Wchnschr.* **33**:904, 1920.

75. Zondek, H.: *Verhandl. f. inn. Med. u. Kinderh.*, Berlin, Jan. 7, 1929; abstr., *Klin. Wchnschr.* **8**:425, 1929.

76. König, W.: *Klin. Wchnschr.* **8**:634, 1929.

77. Glaser, F.: *Med. Klin.* **20**:1237, 1924.

Tomasson⁷⁸ published the most extensive work, studying the mineral metabolism of a large series of psychopathic patients. From his studies he concluded that the calcium fluctuations precede periods of mental instability and that they are inversely proportional to the mood of the patient. In the maniacal periods of maniac depressive insanity, the calcium in the serum is increased and he did not find any low values. Movement in itself is not responsible for this, although under hypnosis there is some lowering of the level. Alterations of the mineral equilibrium of the serum which Tomasson described would be indicative of a loss of calcium from tissues with a coincident penetration by potassium. With it, he found a slight alkalosis.

Hoff and Werner's⁷⁹ experiments indicate that in the neurotic patient one is dealing primarily with a lowering of the threshold between the vegetative and psychic centers, leading to obvious instabilities.

Kraus⁸⁰ definitely grouped "neurasthenia" as a vegetative disturbance, i. e., vagolability, electrolytic alterations not only being associated with the vegetative-neurotic stimulation but determining the type of the reaction.

Regarding the vegetative status as the fundamental background of all reactions, reproductive, developmental—irritability, in general—he conceived the neuroses as distinctly constitutional (as, clinically, they obviously are) with general psychic manifestations, or as organ neuroses with local vagotonic or sympathetotonic overbalance. He assumed that it is potassium which plays the large rôle—nonionized potassium going over to ionized forms on stimulation; this would correspond with our observations. Insofar as the ultimate status of the individual (vital periodicity, reactivity) is, in its final analysis, the result of a balance between cosmic (external) and internal stimuli, we can understand that the constitutional status plus the conditioning effects influence the psychic reactions just as they would any other organ or tissue.

While there seems little doubt that we may legitimately associate changes in the permeability with functional changes in the nervous apparatus, the converse, that the nervous system may change the permeability of the capillaries is also probable; we may be dealing with a circular mechanism.

We have repeatedly stated that the stimulation of the sympathetic side of the autonomic nervous apparatus is associated with diminished

78. Tomasson, Helgi: *Undersøgelser over nogle af blodets elektrolyter (Ca, K, Na, H) og det vegetative nervesystem særlig hos patienter med maniodepressiv psykose*, Copenhagen, Levin & Munksgaard, 1927.

79. Hoff, Hans, and Werner, Paul: *Klin. Wehnschr.* 7:346, 1928.

80. Kraus, F.: *Klin. Wehnschr.* 6:537, 1927.

capillary permeability. Vessels that have been deprived of their sympathetic innervation are more permeable.⁸¹

The work of Gellhorn,⁸⁴ definitely proving the increased permeability following pilocarpine and diminution following epinephrine, is in line with related demonstrations by many observers. We would, however, call attention to the fact that these effects are probably direct effects on the cell membranes. With thyroid and sex hormones increasing permeability (the observations of Asher, Gellhorn, Fröhlich and Zak⁸² and others are convincing) and epinephrine and pituitrin diminishing permeability, and with a regulatory effect of the nervous system in controlling the output of the glands of internal secretion made probable, we can understand that an overflow of nervous impulses to such glands in certain persons would change tissue permeability. Asher and Pfluger⁸³ demonstrated increased activity of the thyroid gland under such conditions. This would in turn increase capillary permeability in general.

There is a close parallelism between "nervousness," capillary permeability, permeability of the meningeal barrier and the K/Ca ratio. In the menstrual cycle, the nervous manifestations are clinically obvious. The related blood chemistry has been well developed.⁸⁴ Heilig and Hoff⁸⁵ demonstrated the increased permeability of the meninges, and we have shown an increase in capillary permeability.⁴⁸ In our present series, the "nervous" persons have, in general, a distinct increase in permeability and with it, as a group, a low K/Ca ratio.

We have had the impression for a number of years that mental instability can result from changes in the ionic equilibrium and from changes in the capillary permeability, just as such alterations may change the reactivity of other tissues in the body. In a woman with a puerperal psychosis, for instance, we observed an unusually high capillary permeability.⁸⁶ In another instance, that of an individual in this series, we called attention to the fact that the patient's high capillary permeability occurred during a time of emotional stress incidental to stock market losses.

Perhaps no more striking association of mental disturbances with alteration of the vegetative system (particularly muscular abnormality) exists than in catatonia. Here we have definite evidence of the control

81. Yamamoto, J.: *Biochem. Ztschr.* **145**:201, 1924. Gabbe, E.: *Ztschr. f. d. ges. exper. Med.* **51**:728, 1926.

82. Fröhlich, A., and Zak, E.: *Klin. Wchnschr.* **8**:1540, 1929.

83. Asher, L., and Pfluger, O.: *Ztschr. f. Biol.* **87**:115, 1929.

84. Riddle, O.: *Proc. Am. Philos. Soc.* **66**:497, 1927.

85. Heilig, R., and Hoff, H.: *Klin. Wchnschr.* **3**:2049, 1924.

86. Petersen, W. F., and Lash, A. F.: *Alterations in Permeability of Skin Capillaries During Pregnancy and Puerperium*, *Arch. Int. Med.* **39**:12 (Jan.) 1927, table 3.

of the clinical picture through ionic alterations. Reese,⁸⁷ together with Loevenhart and Lorenz, demonstrated complete (though transient) restoration of catatonic patients to a normal condition when the latter were stimulated by means of carbon dioxide respiration. Gordonoff and Walther⁸⁸ also showed a marked increase in potassium in the blood and blood corpuscles of such patients.

GLAUCOMA

Our examinations indicate that the patient with glaucoma has a lability of the cardiovascular renal system. This seems in accord with the observations of other investigators. Sulzer's⁸⁹ observations led him to believe that primary glaucoma is due to a vascular disturbance. Schmidt⁹⁰ noted that the water balance of the body is atypical in glaucoma. Thus, in the normal person, the ingestion of water is not followed by a change in eye pressure; in the glaucomatous patient, the pressure is increased. While Schmidt does not believe that the effect is wholly osmotic, he does insist that it concerns a capillary change.

One must, of course, not forget that local anatomic changes—size of the lens, dilatation of the pupil, etc.—are probably the determining factors; the initiation of the disturbance may, however, be closely related to sudden changes in capillary permeability. Goldenburg⁹¹ recently discussed this subject in some detail.

TUBERCULOSIS

Constitution.—The human body reacts fundamentally in two different ways to tuberculous infection: one resulting in a relatively benign process, developing slowly, becoming quiescent through cicatrization and proliferative; the other resulting in an exudative process with fluid effusion, relatively rapid progression and dissolution of tissues. Clinically, we meet every phase of resistance fluctuating between these two extremes, extremes which must depend on differences in irritability of the tissues. The greater the irritability the more marked is the response, the greater the tendency to an exudative process. The less the irritability the greater is the tendency to cicatrization.

With these premises granted, the problem obviously involves the autonomic status of the organism as a whole, the status of the various organs and the question of variations in the vegetative status as modified by the infection.

87. Personal communication to the authors.

88. Gordonoff, T., and Walther, F.: *Klin. Wchnschr.* **8**:1179, 1929.

89. Sulzer, F.: *München. med. Wchnschr.* **75**:768, 1928.

90. Schmidt, K.: *Med. Klin.* **24**:859, 1928.

91. Goldenburg, M.: *Illinois M. J.* **52**:474, 1927; *Am. J. Ophth.* **11**:290, 1928.

It also must be kept in mind that even the acutely exudative process may result in utter destruction, i. e., digestion and removal of the virus and the inflammatory exudate. This latter method is probably a common method of disposal of the smaller lesions, much more common, than mere clinical observation would lead one to suspect.

Of course, the relation of "constitution" to tuberculosis is involved in this problem and is one that has interested physicians since time immemorial. The difficulty has been the definition of the term "constitution." In this way the "asthenic," "phthisical," "respiratory" type of the French has always been stamped as that of the potentially tuberculous person.

Borchardt⁹² discussed the reactivity of the tissues to tuberculous infection in relation to constitutional types. In the "Status-Irritabilis" of Wunderlich, he found more localization in the mucous membranes, the skin, the serous membranes, etc., with a relatively good prognosis and good connective tissue reactions. In the "asthenic" type (Stiller) or the lymphatic arthritic type (Pfaundler) there is apparently a lessened reaction. We are dubious concerning the value of such classifications of constitution for the reason that in the adult the genotype must be greatly modified by the conditioning factors. One of the most important of these we consider to be the probability of a relatively long established preexisting tuberculous infection dating, not infrequently, from childhood. The tuberculous adult who is finally classified as of the "asthenic" or "phthisical" type must frequently be what he is—physically, physiologically and psychically—because of this infection.

While one ordinarily thinks of constitution in its more tangible form, one forgets the possible constitutional differences in the organ reactions and tissue reactions. Thus a congenital deficiency may indeed be expressed anatomically in the structure of the elastic tissue of an organ or in a certain degree of infantilism or in the more rapid senescence that one sees commonly in the teeth or the hair or the structures of the eye in certain families.

The Autonomic Status.—Considerable literature has developed that deals with the autonomic nervous system and tuberculous infection. In this country, Pottenger⁹³ has for many years pioneered in studying symptomatology with particular relation to the underlying autonomic alteration. There is no uncertainty concerning this phase of the problem nor is there any question concerning the general autonomic instability as expressed in the reactions of the vasomotor, the gastro-intestinal and the mental apparatus. Redeker⁹⁴ has but recently reemphasized the

92. Borchardt: *Deutsche med. Wchnschr.* **47**:1159, 1921.

93. Pottenger, F. M.: *Symptoms of Visceral Disease*, St. Louis, C. V. Mosby Company, 1929.

94. Redeker, F.: *Beitr. z. Klin. Tuberk.* **70**:259, 1928.

general psychic instability as part of the reaction of the tissues to the invading organism. A most interesting histologic confirmation has come from Michejew and Pawljutschenke,⁹⁵ whose conclusions we shall quote at some length:

The patho-physiological explanation of the clinical findings in tuberculosis is often most conflicting, due we believe, to incomplete methods of examination. There is no doubt, however, that the tuberculous processes bring about changes in the functions of all organs, not only directly, but indirectly, through pathological alterations of the vegetative endocrine correlations. The entire "vegetative system" in the sense of Zondek-Kraus is destroyed. . . .

Our examinations show that the tuberculous processes bring about diffuse changes in the vegetative centers. It is therefore impossible to associate definite vegetative findings with strictly limited anatomical lesions. We assume furthermore that in the central nervous system, no fixed centers for every type of metabolic activity exist, but that we deal rather with the projection of certain physico-chemical processes on certain nuclei. The diffuse character of the lesions found by us lead us to suspect that in tuberculosis, certain alterations exist that accelerate the penetration of the toxin into the central nervous system.

Leaving aside the factor of predisposition or constitution, we should like to point out that one of the chief factors must be this increase in permeability of the "hematoencephalic" or "capillary" barrier which makes possible this effect of toxin on the central nervous system. It is not necessary to dwell on the change in the concentration in calcium as one of the factors involved in this alteration.

The complexity of the balance between the individual vegetative system and the infection accounts for the multiplicity of symptoms and the variety of symptom complexes in tuberculosis.

It seems probable that the early change in the permeability of the "barrier" plays a rôle in the early appearance of certain nervous manifestations which we may regard as pre-tuberculous.

Changes in general cellular permeability apparently alter chronaxia, for Förster²¹ has shown that it is lowered by epinephrine, calcium chloride and parathyroid, and increased with hydrochloric acid, pilocarpine, choline, thyroxin, etc., and Förster ascribed periodic fluctuations in sensitivity to impulses to alterations in chronaxia brought about by general changes in the permeability. Lapique and his co-workers⁹⁶ had previously demonstrated this phenomenon. Both peripheral and cerebral changes in permeability apparently directly influence the nervous response, and the dependence of the effect of the impulses on the state of the organ has been discussed previously at length.

With the recognition that the local autonomic status of the tissues is of importance in the resistance to tuberculosis, the study of that status has concerned a number of workers.

95. Michejew, W. W., and Pawljutschenke, E. M.: *Arch. f. Psychiat.* **84**:227, 1928.

96. Lapique, M.: *Soc. de biol. Paris* **74**:32, 1913. Obre', A.: *ibid.* **88**:585 1923. Florkin, M.: *ibid.* **97**:1804, 1927.

Eppinger and Hess⁹⁷ were the first to point out that the majority of tuberculous patients give a "vagotonic" reaction to epinephrine. Deutsch and Hoffman⁹⁸ reported that the patient with early tuberculosis gives a "sympatheticotonic" reaction to epinephrine. Later, the reaction is more irregular, with "vagotonia" preponderating. Dresel⁹⁹ confirmed this observation.

A most extensive series of observations was reported by Guth,¹⁰⁰ whose interpretation, in general, follows the line of Danielopolu. He noted that tuberculotoxin acts amphotropically, first irritating both components, later leading to a depression, with emphasis on the vagus side. In general, most of the exudative patients were found to be "vagotonic"; most of the productive types, "sympatheticotonic."

Glaser's study,⁷⁷ as well as Kading's¹⁰¹ work, indicates that the chronic tuberculous person is "sympatheticotonic." Pende¹⁰ came to the conclusion that if the tuberculous person is first "sympatheticotonic" and then becomes "vagotonic," the prognosis is poor, whereas if the tuberculous person is primarily "vagotonic," the process is usually relatively benign. Géza,¹⁰² on the other hand, found "vagotonia" occasionally present with some productive forms.

Kamsler¹⁰³ studied the vascular response to epinephrine, atropine and neucisol in a group of tuberculous patients. He was careful to make the tests only in men and at the same time of the day. He found no apparent relationship between the vegetative response and the prognosis, but noted that the pyknic types responded with low blood pressure curves.

Interesting is his agreement that the vegetative response to these various pharmacologic agents is merely one of an accentuation of a pre-existing orientation and that it is dependent particularly on calcium concentration. He insisted that one should speak merely of an irritability or a depression of the vegetative system, as did Bovet.¹⁰⁴

The autonomic status as judged on the basis of the blood pressure response to epinephrine in our series indicates a decided lessening of the reactivity of the tuberculous group as contrasted with the group of 100 normal persons. So, too, of the twenty-four patients who died, those who lived the longest had the more marked "sympatheticotonic"

97. Eppinger, H., and Hess, L.: *Die Vagotonie*, Berlin, 1910.

98. Deutsch, F., and Hoffman, O.: *Wien. klin. Wchnschr.* **26**:569, 1910.

99. Dresel, K.: *Ztschr. f. klin. Med.* **101**:70, 1924.

100. Guth, E.: *Beitr. z. Klin. d. Tuberk.* **53**:94, 1922; **54**:186, 1923; **55**:33, 1923; **60**:39, 1924. Glaser, W.: *Ibid.* **55**:390, 1923.

101. Kading, K.: *München. med. Wchnschr.* **71**:225, 1924.

102. Géza, Gali: *Gyógyászat* **62**:232, 1922; abstr. *Zentralbl. f. d. ges. Tuberc. Forschung* **19**:31, 1923; **22**:493, 1924.

103. Kamsler, A.: *Klin. Wchnschr.* **7**:110, 1928.

104. Bovet, A.: *Schweiz. med. Wchnschr.* **58**:483, 1928.

reactions to tuberculin when they were examined, and of the four patients who were losing weight at the time of examination but subsequently improved, three showed a "sympatheticotonic" reaction.

We have repeatedly expressed our reservation concerning the use of the terms "sympatheticotonic" and "vagotonic." We should much prefer to discard them entirely, resolving the term into the various components, i. e., the local status of the tissues, whether active or resting, whether with increased or diminished permeability, whether with dilatation or constriction of the vessels, whether with relative alkalosis or relative acidosis, etc. The terms "sympatheticotonic" and "vagotonic" are altogether too conflicting and too broad to be useful.

We shall examine the local reaction from this point of view. About a tuberculous focus there exists a zone of tissue stimulation (irritation) which may range from slight and transient effects that are promptly reversed by the more remote cells of the focus, through all the stages of fatigue and finally to death. In the stage of stimulation, the metabolic rate, acidity, permeability, cellular exchange and enzymatic (digestive) processes, are all increased; calcium leaves the tissue and sodium and potassium enter. A general lessening of tissue cohesion takes place. In general terms, we can regard this as an abnormal status of the vegetative balance in which the autonomic nervous system, the ionic equilibrium, the hormones and the tissue metabolites play their rôles.

Tissue changes associated with autonomic derangement are usually associated with local injury, more rarely with changes in the entire organ and sometimes with alterations in the vegetative balance involving the entire body.

1. Alterations in the nervous component of the vegetative system may originate from (a) purely psychic effects, (b) direct injury of nerves, as for instance, the pressure of enlarged mediastinal glands on the vagus, and (c) central (midbrain) injury, illustrated strikingly in some cases of postencephalitic parkinsonism and in some of the intoxications that follow bacterial or other poisoning.

2. Endocrine dysfunction plays a rôle. Diminution of the suprarenal secretion and perhaps of the pancreatic hormone would have a tendency to increase permeability, as would hyperfunction of the sex glands and of the thyroid gland. The activity is, however, conditioned to a large extent by the ion equilibrium existing at the cell surface, i. e., by the preexisting state of activity of the cell.

3. Tissue reaction is also involved. Increased acidity increases permeability, and this goes hand in hand with a release of calcium from the cells.

The Vascular Reaction to Tuberculin.—Given this background, let us examine the status of the tuberculous tissue and the tuberculous

person as a whole. We know, in general, that the reaction of the tuberculous tissue, as recently shown by Schade and Claussen,¹⁰⁵ is on the acid side (from p_H 7 to p_H 7.3) and exactly at the optimum for growth of the tubercle bacillus. We know, too, that the peripheral dilatation of blood vessels depends not on central vasomotor regulation, but on the peripheral effects of dissimulation, including primarily, increased acidity, as well as the effects of histamine and acetylcholin.

Fleisch recently added a demonstration which is most convincing.¹⁰⁶ Tuberculin itself always causes vessels to dilate.

In preceding discussions, we have pointed out that stimulation of smooth muscle (in the metabolic and membrane sense) is associated with relaxation, i. e., lengthening of the cell. The reason for this seemingly paradoxical point of view we need not again elucidate; the physiologic observations have been generally accepted. When we extend this to the smooth muscle of the blood vessel wall, direct stimulation of cells must result in the dilatation of the vessel. Epinephrine, which makes the membrane less permeable, apparently causes contraction, irrespective of its presumable effect via the sympathetic mechanism.

Tuberculin stimulates the normal organism;¹⁰⁷ in the tuberculous animal, the stimulation may proceed to fatigue. We should expect that in the isolated vessel preparation perfusion with tuberculin would cause dilatation. Experiments of Preobraschewsky¹⁰⁸ are now available on this point. He found that tuberculin causes the normal vessels to dilate, with contraction following. In the tuberculous animal, the preliminary dilatation persists indefinitely. Buillion acts like tuberculin.

He also observed that a vessel preparation of animals with advanced tuberculosis showed a lessened reactivity to epinephrine. We believe this to be explained on the basis of the well known observation that epinephrine causes little or no contraction of vessels in irritated (inflammatory) regions. When tuberculin was injected into animals and vessel preparations were then perfused, the reaction to tuberculin (and buillion) was irregular. Similar experiments were made by Friedberger and Seidenberg.¹⁰⁹

Here a physiologic preparation offers the counterpart of the intravital phenomena that take place when tuberculin is injected or that must obtain when tuberculin is released from a focus. The vessels are

105. Schade, H., and Claussen, F.: *Beitr. z. Klin. d. Tuberk.* **62**:300, 1925.

106. Fleisch, A.: *Klin. Wchnschr.* **8**:1315, 1929.

107. Levinson, S. A., and Petersen, W. F.: *Am. Rev. Tuberc.* **15**:681, 1927.

108. Preobraschewsky, A. M.: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **63**:132 and 139, 1929.

109. Friedberger, E., and Seidenberg: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:276, 1927.

directly stimulated. In place of a normal reversal occurring, the tissue is readily fatigued and reversal is delayed, i. e., dilatation persists.

Therapeutic agents that have been useful in tuberculosis are those most frequently directly active on the capillaries, and even that most specific agent, tuberculin, is effective in the therapy of tuberculosis probably not because of its immunologic properties but because of its influence on the caliber of the arterioles and the permeability of the capillaries (and tuberculous lesions), as originally supposed by Moro.

It is the vascular reaction that must always be regarded as the basis of any understanding of the tuberculous lesion. Physiologic vascular processes, which can be interpreted on the basis of stimulation, of rest or of fatigue, have been disguised by obtuse and conflicting immunologic concepts. We have come to consider resistance without reference to specific concepts, and Kalbfleisch¹¹⁰ seems to have reached the same position when he stated that there is no room for the term "immunity" in the pathology of tuberculosis. This is quite apart from the persistent attack on the specificity of the tuberculin reaction.¹¹¹ We have felt justified in concluding from our experiments¹¹² that the reaction of the normal animal differs from that of the tuberculous animal only in degree. Kalbfleisch's conclusions in this connection are as follows:

There is only one thing that differentiates the effect of tubercle bacilli in tuberculous animals from the effect in the healthy animal; these are differences in the reaction of the vascular system, which, depending on susceptibility to the irritation and reactivity of the nervous elements of the vascular bed of the tuberculous animal, bring about quantitative differences from the reaction of the normal animal, and thereby bring about quantitatively altered effects in the cells and fibers of the tissue.

All the therapeutic agents of the "reactive" class, tuberculin, sodium aurothiosulphate, hetol, etc., act seemingly in a relatively simple way.¹¹³ They first make the tissues more permeable, and later the tissues become less permeable for a considerable period of time.

The focal reaction, whether in the form that is obvious clinically or consisting merely of the imperceptible biologic actions following the injections of minute doses of the agents in question, is a reaction that depends on changes in permeability of the capillaries about the tuberculous focus.

110. Kalbfleisch, H. H.: *Beitr. z. Klin. Tuberk.* **70**:465, 1928.

111. Selter, H., and Bloomenberg, W.: *Beitr. z. Klin. d. Tuberk.* **66**:105, 1927. Beiling, R., and Keller, W.: *ibid.* **69**:577, 1928. Keller, W., and Dölter: *ibid.* **60**:444, 1928.

112. Petersen, W. F.; Jaffe, R. H.; Levinson, S. A., and Hughes, T. P.: *J. Immunol.* **8**:387, 1923. Petersen, W. F., and Levinson, S. A.: *Am. Rev. Tuberc.* **8**:122, 1923.

113. Levinson, S. A.; Petersen, W. F., and Milles, G.: *Am. Rev. Tuberc.* **16**:285, 1927.

Biologic processes, such as the menstrual cycle, the effects of season, etc., that are associated with an increase in capillary permeability and autonomic imbalance are apt to be associated with clinical activation.

A most enlightening condition concerns the relation of the mortality from tuberculosis to the season. The association of clinical activity with the spring goes back to Hippocrates. A recent statistical correlation is that of Herrup from the Faroe Islands.¹¹⁴ The change in the K/Ca ratio and the seasonal changes in the size and activity of the organs made apparent in the work of Riddle¹¹⁵ and Brown⁹ bring us nearer a logical explanation of the clinical observations.

Clinically advancing tuberculosis is associated with increased capillary permeability; healed tuberculosis with diminished permeability. It might seem warranted to draw the conclusion that increase in capillary permeability, however produced, would unfavorably influence a tuberculous lesion, and that, conversely, diminished permeability must be associated with improvement.

We shall not endeavor to include in this summary a review of all the results of the examinations made, but shall discuss briefly only the more important phases of the work.

Correlations Based on Clinical Classifications, Weight Curve, Clinical Prognosis and Fatalities.—The Clinical Classifications of the National Tuberculosis Association (table 2, part VII A): Apart from the obvious correlations (tuberculosis fixation, Daranyi reaction, basal metabolic rate, pulse rate, etc.), there are no consistent changes as we proceed from the incipient A to the far advanced C cases. We might anticipate this. The incipient A group will include patients in whom the disease may develop rapidly, may heal or may become chronic. The far advanced C group will include patients who have had chronic tuberculosis for years, with relatively high resistance. In addition, there will be many persons with febrile tuberculosis, with peripheral vasoconstriction, made evident in the prolongation of the blister time.

Weight Curve (table 3, part VII A): The grouping of patients by relative increase or decrease of weight at the time of examination begins to offer something more tangible. It is to be noted that the persons with healed tuberculosis (roentgen shadows only) have a permeability of 65. Persons with roentgen evidence of active tuberculosis (very chronic) have a permeability of 59. Our sanitarium group shows a progressive increase to 69.6. There is, however, no consistent relation to the blood chemistry, but the blood proteins increase, and the McClure-Aldrich test is markedly shortened.

114. Herrup: Beitr. z. Klin. d. Tuberk. 68:739, 1928.

115. Riddle, O.: Am. Naturalist 61:481, 1929.

Prognosis (table 9, part VII A): Here we begin to obtain interesting clinical and laboratory correlations. The relation to permeability and to calcium has been discussed. We note that the "vagotonic" reaction to epinephrine increases, the epinephrine flare becomes smaller while the thyroxin flare becomes larger, the cholesterol/lecithin ratio becomes smaller, the McClure-Aldrich test becomes shorter and the tuberculin reaction smaller.

Fatalities (table 10, part VII A): When, finally, we consider the patients who died and place them in two groups, (those that lived an average of forty-five months after the onset of clinical activity and those that lived an average of sixty-five months), we find that the less resistant group had a high capillary permeability, much less calcium, less cholesterol, a higher globulin content and a shorter McClure-Aldrich time, while there were more "sympatheticotonic" persons in the group that lived longest.

Calcium.—We must regard the calcium metabolism as in some way closely associated with the clinical condition of the patient. In the group with low calcium, for instance, we find more deaths. We find that the persons with healed tuberculosis have higher calcium (10.3), that persons with good prognosis have higher calcium (10.7 and 10.6), that those with stationary disease have lower calcium (9.1); as we then turn to those with poor prognosis, the calcium level again rises (10.2), owing, we believe, to the probability that with a negative balance, calcium is being mobilized from the tissues. We have previously discussed some of the literature dealing with calcium in tuberculosis (part III).

More and more clinical evidence is accumulating which indicates the importance of calcium in tuberculosis in regard to both the reactivity of the tissue and its influence on the disease process. Sternberg¹¹⁶ found lower serum calcium in the most advanced cases; Schaefer,¹¹⁷ an increase in the calcium in the lung in chronic tuberculosis. Sweany¹¹⁸ and his associates found the calcium levels about normal, and Hoyle,¹¹⁹ admitting the clinical impression of improvement with calcium, regarded the experimental evidence as still lacking. He found an early increase in calcium in rabbits infected with tuberculosis, with a terminal decline. The lack of experimental confirmation is, however, not necessarily a criterion of clinical value, for the reason that tuberculosis in the guinea-pig and in the rabbit, particularly, is decidedly different from tuberculosis in man. As a matter of fact, Henner¹²⁰ observed that when

116. Sternberg, T.: Beitr. z. Klin. d. Tuberk. **71**:737, 1927.

117. Schaefer, R.: Beitr. z. Klin. d. Tuberk. **69**:86, 1928.

118. Sweany, H. S.; Wethers, A. T., and McCluskey, K. L.: Am. Rev. Tuberc. **8**:405, 1924.

119. Hoyle, J. C.: Quart. J. Med. **22**:451, 1929; J. Pharmakol. & Exper. Therap. **34**:317, 1928.

120. Henner: Beitr. z. Klin. d. Tuberk. **51**:56, 1929.

calcium dust ($\text{Ca}[\text{OH}_2]$) was used, tuberculous animals not only showed less involvement than animals exposed to other dust, but actually less than the control animals not exposed to dust. The clinical literature, as mentioned previously, is rather conflicting, and various methods have been suggested for the administration of calcium, as well as various indications. Thus Siegel¹²¹ stated that he obtained improvement in 50 per cent of his cases with calcium inhalation. Becker¹²² treated 150 patients with intravenous medications and mentioned improvements, particularly in bilateral involvements.

Cholesterol.—That cholesterol usually diminishes with progressive tuberculosis has been frequently noted. This, of course, is in line with the change in cholesterol metabolism apparent in other infections.¹²³ In recent work, Shope¹²⁴ brought experimental evidence that increasing serum cholesterol probably plays some rôle in prolonging the life of experimentally infected guinea-pigs, confirming clinical observations that date back a number of years.¹²⁵ Borchardt,¹²⁶ as well as Leupold and Bogendorfer, recently presented further experimental evidence concerning the usefulness of cholesterol in increasing resistance to infection, an increase which seems to follow specific immunization, too.¹²⁷ The association of a low cholesterol in tuberculosis with poor prognosis was noted by Rieter,¹²⁸ and is in line with the results of our observations.

It is rather interesting to note that Glaser¹²⁹ published clinical observations indicating that the cholesterol level of the blood may change with changes in the psychic state just as does the calcium level, while Wade¹³⁰ found an increase in cholesterol associated with a decrease in the serum calcium.

Reactivity of the Skin.—The reactivity of the skin of the tuberculous patient has been a subject of study for so many years by so many investigators that we shall make no effort to review the literature, but merely point out that there is a general recognition of the fact that, apart from the so-called "specific" factor, the degree of reactivity is dependent on the status of the skin, i. e., that the systemic factors play a decided rôle. Thus, the reactivity to tuberculin diminishes in the

121. Siegel, H.: Ztschr. f. Tuberc. **53**:256, 1929.

122. Becker, A.: Ztschr. f. Tuberc. **53**:198, 1929.

123. Heening, B. H.: J. Biol. Chem. **53**:167, 1922. Gabrila, J., and Vior, V.: Arch. d. mal. de l'app. digestif **18**:601, 1928. Heinze, V.: Ztschr. f. Tuberc. **52**:199, 1928.

124. Shope, R.: J. Exper. Med. **46**:321, 1928.

125. Valois, G.: De la cholesterinene an cours de la tuberculose pulmonaire, Lyon and Paris, A. Maloine et fils, 1912. Farini, A.: Gazz. d. osp. **35**:993, 1914.

126. Borchardt, W.: Klin. Wchnschr. **8**:1179, 1929.

127. Barbara, M.: Arch. di pat. e clin. med. **8**:379, 1929.

128. Rieter, H.: Klin. Wchnschr. **8**:1158, 1929.

129. Glaser: Klin. Wchnschr. **6**:2377, 1927.

130. Wade, P. A.: Am. J. M. Sc. **177**:790, 1929.

terminal stages in tuberculosis, during intercurrent disease and with "desensitization" due either to tuberculin therapy or as a result of non-specific injections.

Nor is it possible to review the extensive literature concerning reactivity of the skin, in general. The monographs of Lewis,¹³¹ the shorter works of Hecht,¹³² Pulay¹³³ and Luithlen,¹³⁴ the reviews of von Groer⁴⁶ and Ebbecke¹³⁵ are available for this purpose.

We would, however, refer again to the work of Kauffmann.⁵² Kauffmann observed that when he placed cantharides on the skin of a patient with pneumonia, several distinct stages of reactivity could be distinguished. First, during the febrile period, he observed a delayed or absent reaction. Second, with defervescence a marked reaction; third, after defervescence, a period of transition during the next ten days to a maximum monocytic reaction in the exudate; fourth, for a varying interval, another period of inhibition or delayed reactivity (adaphorea of von Groer, presumably not the same as local immunity in the specific sense).

As cantharides constitute a chemical irritant acting primarily on the cell membranes, specific sensitization plays no rôle, but the results are nevertheless of interest for the tuberculin reaction. Let us examine the possible correlation.

1. During the febrile stage there exists a peripheral inhibition (vasoconstriction). Cantharides can act on the cells, but little or no exudate forms. The direct injury to the cells is great because there is no dilution, and healing takes place slowly (see discussion of herpes). Applied to tuberculosis and the tuberculin reaction, it means that during the febrile stage of an intercurrent disease, the tuberculin reaction is inhibited because of the change in the status of the skin; during the terminal stages of tuberculosis itself, this factor is also operative.

2. During the period corresponding to defervescence in pneumonia when, as Meyer pointed out, vascular dilatation is accentuated, this peripheral factor is negated, and vigorous reaction takes place. Applied to the tuberculin reaction, this corresponds to the period of maximum response when sensitization (i. e., direct cellular response and vasodilatation due to the direct effect of the tuberculin) prevails at a time during which peripheral vasodilatation is compensating for the increased metabolism going on in the body, i. e., during the period of vasomotor

131. Lewis, T.: *The Blood Vessels of the Human Skin*, London, Shaw & Sons, 1927.

132. Hecht, A. F.: *Ztschr. f. d. Ges. exper. Med.* **33**:23, 1923.

133. Pulay, E.: *Stoffwechsel und Haut*, Vienna, Urban & Swartzenberg, 1923.

134. Luithlen: *Pharmakologie der Haut*, Berlin, Julius Springer, 1921.

135. Ebbecke, U.: *Deutsche med. Wchnschr.* **50**:1, 1924; *Naturwissenschaften* **14**:1131, 1926.

instability, when the tuberculotoxin has not yet stimulated the liver to the degree that the splancho-peripheral balance has become fixed. The autonomic skin function is, in other words, practically normal insofar as lability is concerned.

3. Finally, in the pneumonia patient, at varying intervals after the crisis (from three to five weeks), a period supervenes during which the skin is again nonreactive. Here we are not dealing with a peripheral vasoconstriction present during the acute febrile stage. The tissue cells have changed. The cell membranes are no longer irritated to the same degree by the same amount of the irritant. The cell membranes have become less permeable. Applied to tuberculosis we find the same picture during periods of relative quiescence of the lesions, with recovery; after a course of tuberculin treatment, or after a series of relatively bland nonspecific injections.

These are wholly nonspecific effects which influence the reactivity of the skin in general, but they are of importance for the problem of tuberculosis because the vegetative status of the skin and the vasomotor activity are underlying factors that determine the type of reaction to all toxic agents.¹³⁶

That these different states of reactivity of the skin are associated with differences in the underlying physicochemical equilibrium we need not again emphasize. However, the experiments of Klauder and Brown,¹³⁷ which are pertinent, must be mentioned. In their experiments, a correlation of the blood and skin chemistry with the intensity of the skin reaction is made evident.

Apparently, differences exist that depend on the type of irritant; for instance, calcium seems to be much more closely related to the effect of epinephrine and to the blister time; potassium, to the effect on the skin of thyroxin and caffeine. Needless to say, there are many other modifying factors (table 1, part I).

Leukocytic Reaction.—Among the reactions that we have followed with particular interest has been the effect of the intracutaneous injection of a bland protein on the leukocytic curve.

136. Roeckemann: Beitr. z. Klin. d. Tuberk. **49**:301, 1922. Stutz: Schweiz. med. Wchnschr. **54**:676, 1924. Schubert, A.: Beitr. z. Klin. d. Tuberk. **69**: 273, 1928.

137. Klauder, J. V., and Brown, H.: Experimental Studies in Eczema: I. A Study of the Sensitivity of the Skin of Rabbits to Chemical Irritants Under Experimentally Induced Conditions, Arch. Dermat. & Syph. **11**:283 (March) 1925; II. A Correlation of the Chemistry with the Irritability of the Skin of Animals Under Normal and Under Experimentally Induced Conditions, *ibid.* **15**:1 (Jan.) 1927; III. The Rôle of Sympathetic Nervous Irritability in the Rabbit, *ibid.* **19**:52 (Jan.) 1929; IV. The Correlation of the Potassium-Calcium Ratio in the Serum and in the Skin of Rabbits with the Irritability of the Skin, *ibid.* **20**: 326 (Sept.) 1929.

Intracutaneous injections bring about systemic effects, not only through the agency of the injected solution, but through the stimulation of the skin. Perhaps this stimulation of the skin is associated with liberation of histamine; perhaps it is due to a purely autonomic upset of the type that we have illustrated in charts 2, 3 and 4. Lewis reported experiments in which multiple areas of irritation of the skin resulted in a distinct systemic effect due, according to his hypothesis, to the actual liberation of enough histamine to bring about a general reaction.

Our composite curves indicate that when patients are classified on the basis of increasing, stationary or decreasing weight, the leukocytic reaction in the losing group is that of a rather marked primary leukopenia following the intracutaneous injection. Such a group of patients shows a coincident lowering of the blood pressure. We ascribe this to the fact that in this group the splanchnic vascular bed is more easily thrown out of balance with consequent accentuation of splanchnic stimulation and dilatation and a resulting accumulation of leukocytes in the splanchnic area. The reactions merely afford additional evidence for the supposition of an altered vegetative status with progression of the disease.

Therapeutic Considerations.—Granted that the tuberculous lesion can be made clinically innocuous in one of two ways—(1) by digestion and (2) by complete encapsulation—the former method would be supported therapeutically by any measures that increase vascularization, increase enzymatic processes, increase permeability or, in general terms, bring about tissue stimulation, with relative acidosis, or the so-called “parasympathetic status.”¹³⁸ The inherent danger lies (1) in the possibility of dissemination of the virus, (2) in the diffusion of toxic products and (3) in the possibility that stimulation may proceed to fatigue and death. We can readily understand that only sluggish lesions of the peripheral type or small lesions in the more vascular organs can be so treated with any degree of safety.

The second method, complete encapsulation, would be supported therapeutically by methods that decrease vascularization, decrease enzymatic processes, decrease capillary permeability or, in general terms, bring about rest of tissue or a “sympathetic” status,¹³⁹ with relative alkalosis. Here one must assume a therapeutic indication in the more extensive lesions, especially of the vascular organs.¹⁴⁰

From the point of view of constitutional types, we can see that our heavy type should offer a general biologic status of diminished permea-

138. To be differentiated from vagotonia (see page 18).

139. To be differentiated from sympatheticotonia (see page 18).

140. The vascular endothelium of the viscera—liver, kidney, spleen, gastrointestinal tract—is normally more permeable than that of the peripheral tissues.

bility, lower metabolic rate and more sluggish inflammatory reactions that would seem favorable for the development of a slowly progressive, relatively benignant lesion. Presumably, in endocrine balances we would see less effect of the thyroid gland, with probably more effect of the pituitary gland, and in some cases more secretion of epinephrine.

Our slender type should offer two possibilities: a person, who, because of intense reactivity—with relative acidosis, increased metabolic rate, increased permeability, etc.—might, under certain circumstances, succumb to the infection rapidly, especially if infected with a large dose of the virus; and another person of the same type who might readily and rapidly dispose of tubercles, with relative freedom from clinical symptoms. The latter would presumably have more thyroid secretion, more sex gland secretion and varying degrees of suprarenal and pituitary activity.

It is perfectly obvious to us that in the intricate biologic picture of inflammation presented by tuberculosis innumerable possibilities exist. We have merely delineated the extremes. We would, however, reiterate that in clinical tuberculosis, it is the vascular mechanism that must always be in the foreground of consideration.

The particular therapeutic studies that have been introduced in the final paper of the tuberculosis series (VII C) are to serve only to illustrate several points in connection with the theoretical deductions; they are not to be regarded as clinical evidence for another cure for tuberculosis. They indicate that:

1. *Pilocarpine* (case of sister A, part VII C), which makes the capillaries more permeable, may be followed by dissemination.
2. *Epinephrine* (case of sister B) which normally is not only diphasic but amphotropic, may, when it makes capillaries less permeable, diminish clinical activity; or may make the capillaries more permeable and increase clinical activity (case 2, under "Reports of Other Cases," part VII C).
3. *Pituitrin*, which apparently acts more specifically on the cell membrane in lessening permeability (even in irritated tissues) may lessen clinical activity (cases 4 and 5).
4. *Alkalosis* is apparently useful (case 1) and stimulation of the skin by means of a skin burn, which theoretically should result in a peripheral dilatation and a splanchnic constriction, may also be useful (case 3).

With investigators in tuberculosis becoming more and more interested in tissue activity as a factor in resistance, many therapeutic procedures will be offered and exploited. The Gerson diet has already been capitalized. Here a diet predominantly of vegetables and fruits with its tendency toward alkalinization is advised with a salt-free oat-

meal diet, with its contrary tendency, and a proprietary salt mixture is added for good measure. Of course, the clinical reports are conflicting. If the Gerson diet really tends to bring about tissue acidosis, it should be useful in the sluggish peripheral types of infection, and actually the results in infection of the skin seem to be encouraging. On the other hand, there appears to be little consistent effect in the pulmonary lesions. As is the case with so many cure-alls the proponents here forget the innumerable individual features of each clinical picture and that a therapy which may be admirable for a sluggish tuberculosis of the skin is by no means necessarily useful for a visceral tuberculosis.

Practically every "cure" has met with this fate, and it must be the fate of every type of treatment that depends on tissue reactivity for its curative properties. "Stimulating" substances—tuberculin, hetol and sodium aurothiosulphate, for example—are active in sufficiently large doses by increasing permeability. And with large doses, injury almost invariably results. In small doses, they are sometimes useful because the transient stimulation and increased permeability are followed by a reversal—with a persisting impermeability. The agents that might presumably act in a contrary direction, epinephrine as originally suggested by Sargent, or calcium, may be useful when the preexisting state of the tissue is favorable. If not, one may get "paradoxical" effects with increased permeability and clinical injury. Even the physical agents, particularly heliotherapy, are followed by identical results. Sunlight may activate lesions in certain persons and may be useful in others.

We have the conviction that if we once begin to plan the therapeutic attack in tuberculosis less from the point of view of the immunologists and pharmacologists and more from that of the inflammatory reaction and its physiologic and physiochemical aspects, we shall be able to devise a more rational therapy.

What has been detailed for a chronic infection like tuberculosis has been presented merely to illustrate a point of view which we believe may be useful in other therapeutic problems.